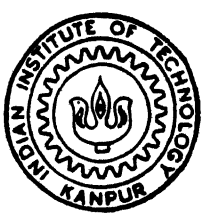
REACTIONS OF CHLOROSULFONYL ISOCYANATE WITH 1-AROYLAZIRIDINES, OXAZIRIDINES AND 2'-AMINOCHALCONES: A SYNTHETIC ROUTE TO FIVE AND SIX MEMBERED HETEROCYCLES

by

PRAMOD KUMAR



DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY KANPUR

February 1994

REACTIONS OF CHLOROSULFONYL ISOCYANATE WITH 1-AROYLAZIRIDINES, OXAZIRIDINES AND 2'-AMINOCHALCONES: A SYNTHETIC ROUTE TO FIVE AND SIX MEMBERED HETEROCYCLES

A Thesis Submitted
in Partial Fulfilment of the Requirements
for the Degree of
DOCTOR OF PHILOSOPHY

by

PRAMOD KUMAR

to the

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY KANPUR
February 1994

CHM-1994-D-KUM-REA

TO

MY BELOVED PARENTS

WITH GRATITUDE

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY KANPUR
CERTIFICATE I

This is to certify that Mr. Pramod Kumar has satisfactorily completed all the courses required for the Ph.D. degree programme. The courses include:

CHM 505 Principles of Organic Chemistry

CHM 524 Modern Physical Methods in Chemistry

CHM 525 Principles of Physical Chemistry

CHM 545 Principles of Inorganic Chemistry

CHM 646 Bio-Inorganic Chemistry

CHM 681 Basic Biological Chemistry

CHM 800 General Seminar

CHM 801 Graduate Seminar

CHM 900 Post Graduate Research

Mr. Pramod Kumar has successfully completed his Ph.D. qualifying examination in September, 1989.

P. K. Ghosh

Professor P.K. Ghosh
Head
Department of Chemistry
I.I.T. Kanpur

Javed Iqbal

Professor J. Iqbal
Convener
D.P.G.C.
Department of Chemistry
I.I.T. Kanpur

CERTIFICATE II

Certified that the work embodied in this thesis entitled, **"REACTIONS OF CHLOROSULFONYL ISOCYANATE WITH 1-AROYLAZIRIDINES, OXAZIRIDINES AND 2'-AMINOCHALCONES: A SYNTHETIC ROUTE TO FIVE AND SIX MEMBERED HETEROCYCLES"**, has been carried out by Mr. Pramod Kumar under my supervision and the same has not been submitted elsewhere for a degree.

D. N. Dhar

I.I.T. Kanpur
February, 1994

Durga Nath Dhar
Thesis Supervisor

STATEMENT

I hereby declare that the work embodied in this thesis entitled, "**REACTIONS OF CHLOROSULFONYL ISOCYANATE WITH 1-AROYLAZIRIDINES, OXAZIRIDINES AND 2'-AMINOCHALCONES: A SYNTHETIC ROUTE TO FIVE AND SIX MEMBERED HETEROCYCLES**", is the result of the investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Kanpur, India, under the supervision of Professor Durga Nath Dhar.

In Keeping with general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

I.I.T. Kanpur

February, 1994

Pramod Kumar

Pramod Kumar

ACKNOWLEDGEMENTS

It is with profound sense of gratitude I place on record my sincere thanks to Professor Durga Nath Dhar for introducing me to the field of Synthetic Organic Chemistry. He gave me continuous support and guidance which enabled me to complete this work.

I wish to express my heartfelt salutations to my mentor Dr.(s) W.E. Wauber, S.C. Srivastava and D.A. Harrison (Christian College Lucknow) who introduced me to Organic Chemistry. My thanks are also due to Prof. V.K. Tandon (University of Lucknow) for his interest in my progress.

I thank my inspiring teachers, Prof. S. Ranganathan, Prof. R.N. Mukherjee, Prof. P.C. Nigam (Retd.), Prof. P.K. Bharadwaj, Prof. S. Manogaran and Prof. S. Chandrasekaran (I.I.Sc. Bangalore) whose teachings on the basic principles of Chemistry will be with me throughout.

I wish to express my thanks to Prof. Franklin A. Davis (Drexel University, Philadelphia, USA) for providing me invaluable literature for my research work.

My sincere thanks are due to Drs. K.P. Madhusudanan, R. Roy and Mr. R.K. Singh (CDRI Lucknow), Messrs Arun Bhavsar and Nayab Ahmed (I.I.T. Kanpur) for recording the spectra of compounds reported in this dissertation.

I wish to extend my special thanks to Prof. S Ranganathan and Prof. S. Sarkar for providing me with their lab facilities during my research work.

I am particularly indebted to my colleague Dr. E. Sampath Kumar for his invaluable assistance in checking the references, discussing the contents and commenting on the manuscript.

I have no words to express my heartfelt feelings towards M/s Arun Goyal and Narendra K. Vaish who helped me a lot.

I would like to thank my friends who made my stay in this campus a memorable one. In this regard I would like to mention the names of the following: Drs. Daniel, Chaudhary, Shukla, Sanjay, Kalra, Reddy, Jayaraman, Jena, Ram Naresh and Messrs Samar, Subrato Roy, Shaji, Kundu, Immie, Kamal, Kashi, Tarakeshwer and Maiti

My personal regards to Mrs. Dhar and Mr. M.L. Gupta and family for their encouraging support and hospitality.

I sincerely acknowledge the help rendered by the staff of Chemistry Department, Glass Blowing Section, Chemistry Stores and the Chemistry Workshop.

I acknowledge my profound appreciation to my wife, Bhavna, for kind understanding, unstinted cooperation and encouragement for the completion of my work.

Finally, my language fails to express my indebtedness to my parents, brothers, sisters and relatives for extending their constant encouragement all through my educational career.

I.I.T. Kanpur — Pramod Kumar

February, 1994

SYNOPSIS

Isocyanates are members of the cumulene family and are important building blocks in organic synthesis. Chlorosulfonyl isocyanate (CSI) **1**, is highly reactive isocyanate and a versatile reagent. This reagent has received considerable attention, since its discovery (Graf, 1952) due to its high reactivity as a uniparticulate electrophile and a heterocumulene in cycloaddition with multiple bonds, small rings and reaction with bifunctional compounds. A major objective of this work is to broaden the application of CSI towards the synthesis of various heterocyclic ring systems. The results obtained in this direction form the subject matter of this thesis.

$O{=}C{=}N{-}SO_2{-}Cl$

1

The thesis is divided into four chapters. Chapter I incorporates a brief overview of the literature covered up to early 1993, regarding the chemistry of CSI. To illustrate the usefulness of this novel reagent in the synthesis of various heterocycles, several reactions have been highlighted which provide an appropriate background material for further research work in this direction.

The chapter II deals with our investigations on the reaction of CSI with oxaziridines. The aim of this work was to know whether oxaziridine on reaction with CSI gives an amide (*via* rearrangement) or yields a cycloadduct (*via* 1,3-dipolar cycloaddition). It was observed that oxaziridines react with CSI in a facile manner to yield the corresponding 4-chlorosulfonyl-1,2,4-oxadiazolidin-5-ones as the sole product. A plausible mechanism involving an oxonium ion formation followed by cleavage of C-O bond of oxaziridine ring and

formation of a stable carbocation has been advanced to explain these experimental observations. The products, namely, 4-chlorosulfonyl-1,2,4-oxadiazolidin-5-ones are obtained in good yields (57-94%) and hence the said reaction can be used as a one-flask method for the synthesis of 1,2,4-oxadiazolidin-5-ones. This chlorosulfonyl derivative can be easily transformed into the corresponding 1,2,4-oxadiazolidin-5-one in good yield, by mild hydrolysis brought about by sodium sulfite and a base.

The study of the reactions of some 1-aroylaziridines with CSI constitutes the subject matter of chapter III of the thesis. The reaction was carried out to know whether 1-aroylaziridine gives a seven membered heterocycle (*via* 1,5-addition) or a usual five membered heterocycle, which is formed by the previously reported reaction of aziridine and CSI. It was observed that 1-aroyl-2,2-dimethylaziridines react readily with CSI, followed by mild hydrolysis, to yield a five membered (3+2) cycloadduct *viz.*, 3-aroyl-5,5-dimethyl-2-imidazolidinones and 2-oxazolines . A reasonable mechanism, involving a seven membered intermediate, has been put forth to explain the formation of 2-imidazolidinone and 2-oxazoline. It has been observed that the presence of an aroyl group on the nitrogen atom does not favour the formation of a stable seven membered heterocycle, instead it reduces the reactivity of aziridine ring system towards cycloaddition with CSI. However, 1-(4-nitrobenzoyl)-2,2-dimethylaziridine reacts with CSI to yield 2-oxazoline derivative as the sole product.

The results of our studies related to the reaction of CSI with 2′-aminochalcones **8** have been incorporated in chapter IV of the thesis. The objective was to synthesize potential bio-active compounds, *viz.*, 2-(1H)-quinazolinones and 1H-2,1,3-

the types of heterocycles have been achieved. A plausible mechanism which could account for the formation of 4-styryl-2(1H)-quinazolinones would involve a nucleophilic attack of amino group of 2'-aminochalcone on the isocyanate group of CSI followed by the cyclization with the carbonyl function. Attack of amino group of chalcone on the sulfonyl group of CSI yields another class of reactive isocyanate. During the work-up the later compound undergoes hydrolysis to produce a sulfonyl urea derivative which undergoes intramolecular cyclization (involving the attack from the nitrogen lone pair of the $-NH-SO_2-NH_2$ function on the carbonyl group) to produce 4-styryl-1H-2,1,3-benzothiadiazine-2,2-dioxide. Alteratively, another mechanism involving the reaction of carbonyl group of chalcone with CSI followed by carbon dioxide elimination and cyclocondensation with amino group has been put forward to explain the formation of 2,1,3-benzothiadiazine-2,2-dioxide derivative.

All the synthesized compounds were characterized by analytical and spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and MASS). These reactions (detailed in thesis) provide a simple synthetic route to some five and six membered heterocycles.

CONTENTS

CHAPTER-I

CHEMISTRY OF CHLOROSULFONYL ISOCYANATE: AN OVERVIEW OF LITERATURE

Isocyanates are important members of cumulene family and are useful building blocks in heterocyclic synthesis. Chlorosulfonyl isocyanate (CSI), **1** discovered by Graf[1,2] in 1952, is the most chemically reactive isocyanate known. The polar chlorosulfonyl group attached to the isocyanate function, enhances the reactivity of the adjacent isocyanate group such that its carbon atom becomes strongly electrophilic. This reagent has received considerable attention owing to its reactivity as a uniparticulate electrophile and as a heterocumulene in cycloaddition reactions.

$$O{=}C{=}N{-}SO_2{-}Cl$$

1

If one conceives chlorosulfonyl isocyanate as an electrophile, there are two sites of attack by an nucleophilic species *viz.*, the carbonyl and the sulfonyl groups. The isocyanate group reacts more rapidly than the sulfonyl group. In addition, the cycloaddition to the C=N bond of cumulative function can also occur. CSI undergoes all three types of reactions.

The chemistry and synthetic applications[3-7] of CSI have been the subject of many reviews. This novel reagent (CSI) finds extensive use in the synthesis of small, large, fused and unusual heterocyclic systems. Reactions of CSI cited in the literature have been

classified mainly based on the site of initial attack by a given nucleophile, *viz.*, type I generally involving the initial attack at the isocyanate moiety , while type II deals with cycloaddition across the C=N bond and type III involves nucleophilic addition at the sulfonyl group. We adhered to the following classification based on the applications of CSI in the preparation of heterocycles.

I.1. Reaction with active hydrogen compounds

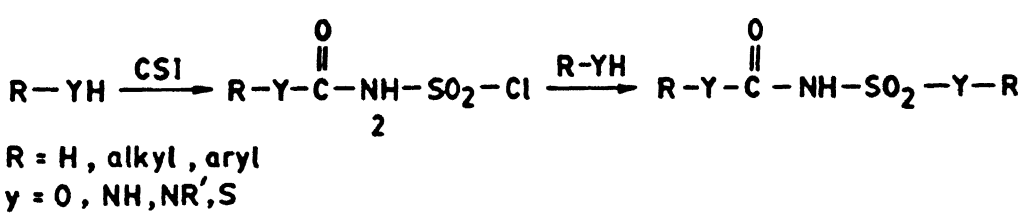
I.2. Cycloaddition reactions

I.3. Reaction with small ring heterocycles

I.4. Miscellaneous reactions

I.1 REACTION WITH ACTIVE HYDROGEN COMPOUNDS

Chlorosulfonyl isocyanate undergoes nucleophilic addition with active hydrogen compounds like, for example, alcohols, thiols phenols and amines[8]. The resulting N-chlorosulfonyl derivative 2 can be easily functionalized by reacting with water, alcohol or amine. Thus, the use of CSI enables the formal insertion of the $CO-NH-SO_2$ moiety between hydroxyl (thiol) and/or amine functional groups.

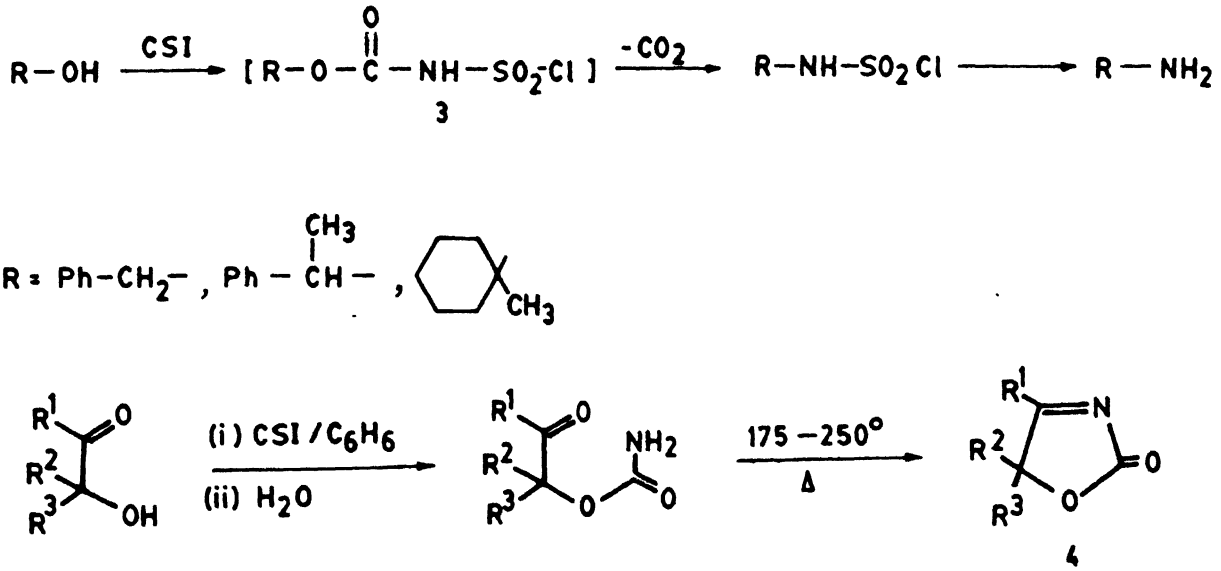


The reaction of CSI with alcohols is quite facile, and this fact has been exploited in their transformation to the corresponding amines[9]. This mainly applies to tertiary and benzylic alcohols, R-OH, in which the alkyl portion, R is able to stabilize a positive charge on carbon atom.

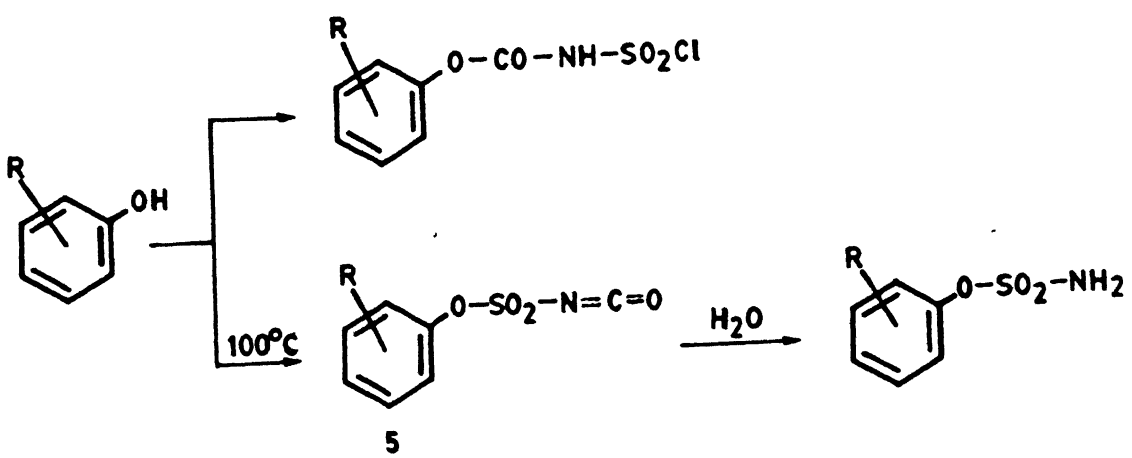
The intermediate 3 was further exploited for the preparation of other heterocycles from readily available starting materials. For example, 2-oxo-2,5-dihydro-1,3-oxazoles (4) can be prepared in good yield by the reaction of α-ketoalcohols[10] with CSI (Scheme I.1.1).

The reaction of phenols with CSI at ordinary temperature is quite analogous to those of alcohols, but at elevated temperature the reaction affords a new class of reactive isocyanates, namely, aryloxysulfonylisocyanates[11] (5) as depicted in scheme I.1.2.

SCHEME I.1.1

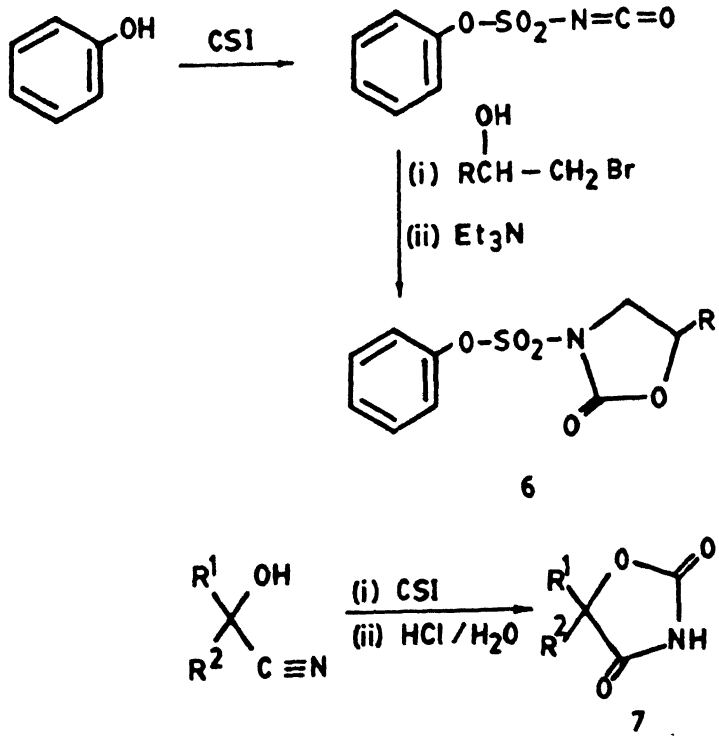


SCHEME I.1.2



Conversion of phenol to phenoxysulfonyl isocyanate (using CSI) and its subsequent reaction with *sec*-bromoalcohol gives the corresponding phenoxysulfonamide, which undergoes smooth cyclization, in the presence of triethylamine, to the oxazolidone[12] **6**. The reaction between cyanohydrins[13] and chlorosulfonyl isocyanate, followed by acid hydrolysis, provides an efficient route for the one-flask preparation of 5,5-disubstituted-2,4-oxazolidinediones (7) (Scheme I.1.3).

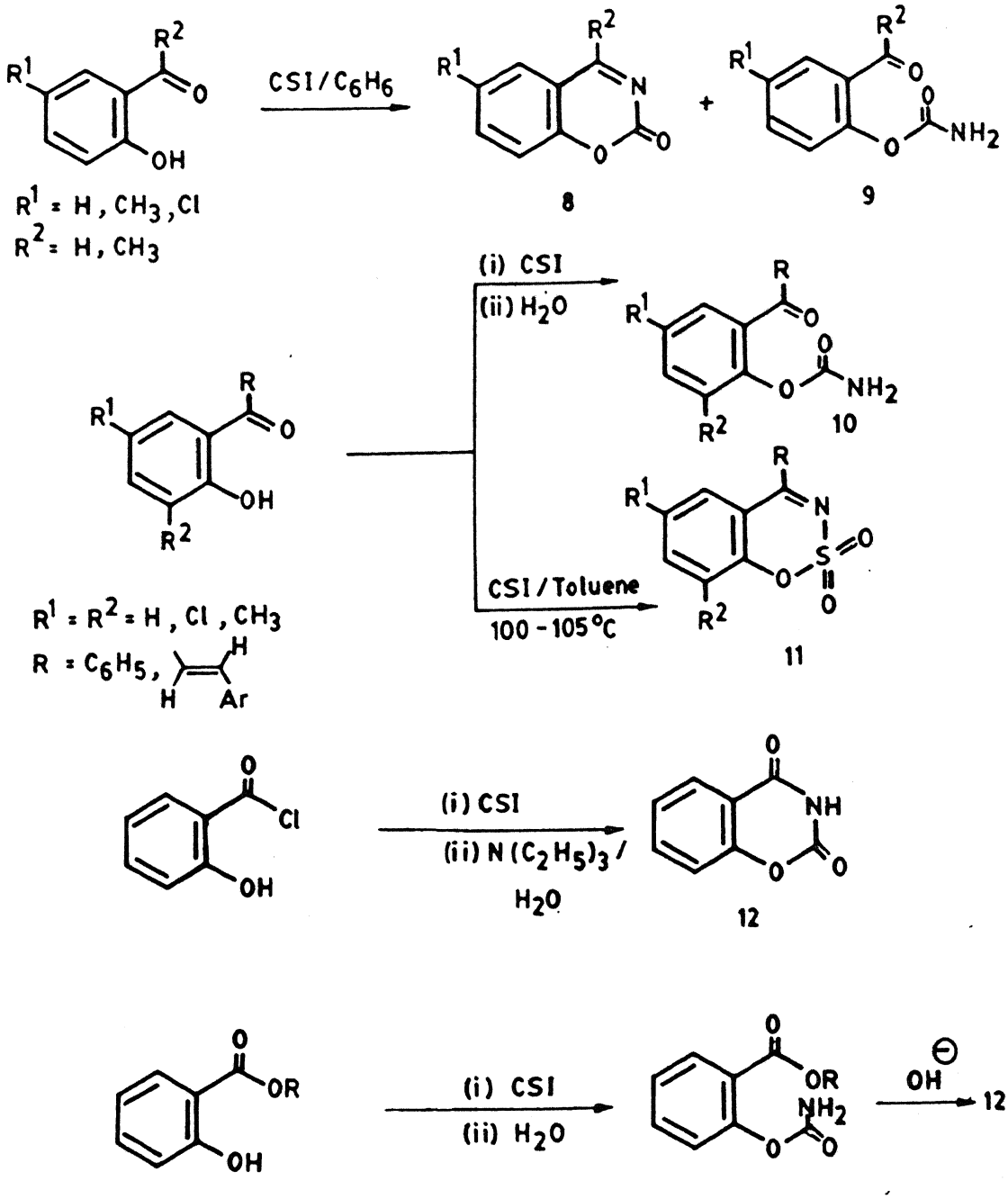
SCHEME 1.1.3



Cyclization of 2-hydroxyaldehydes and ketones with CSI yield the corresponding six membered heterocyclic compounds. Thus, salicylaldehydes and 2-hydroxyacetophenones[14] react with CSI to yield 2H-1,3-benzoxazine-2-ones (8) as major products and *o*-aminocarbamoyl derivatives (9) as minor products. However, 2-hydroxybenzophenones and 2-hydroxychalcones[15] under similar reaction conditions yield only

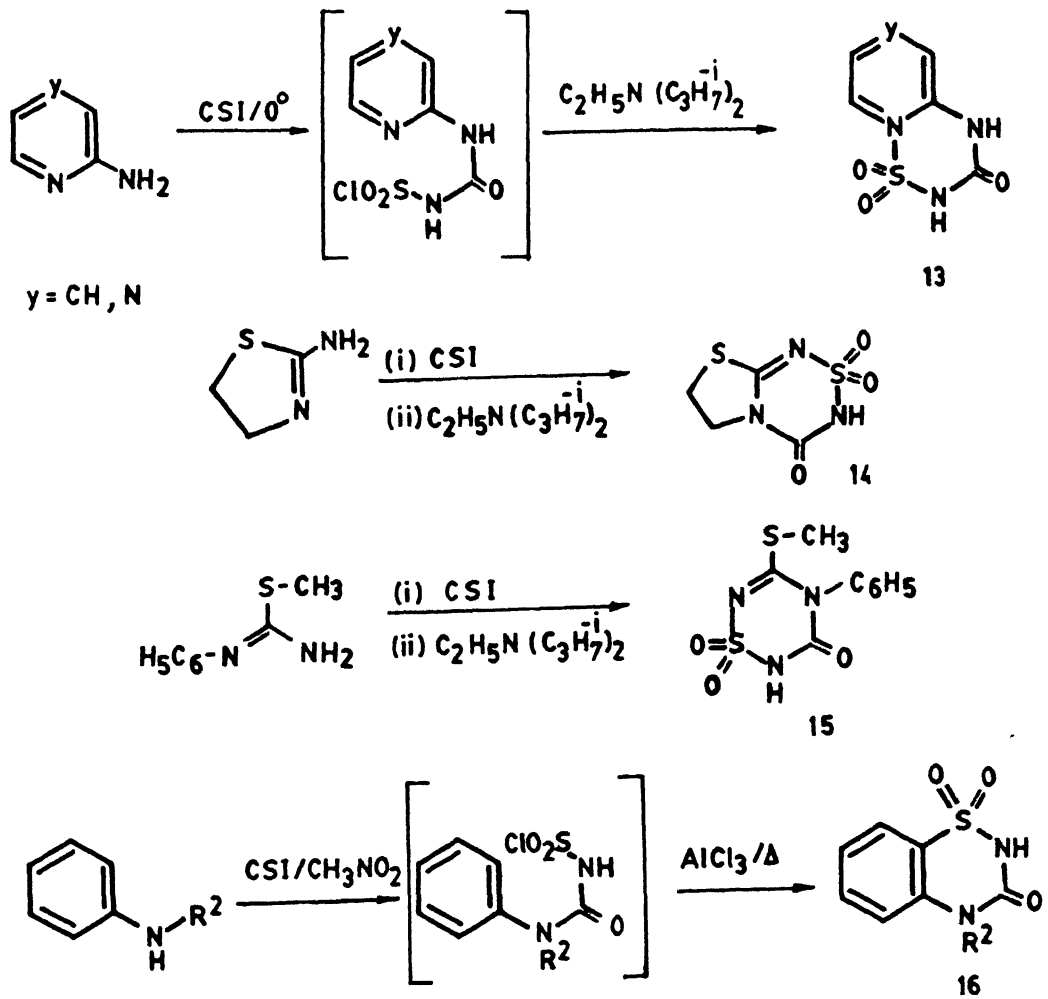
the *o*-carbamoyl compounds (10) in high yields. The same reaction when conducted in refluxing toluene, affords another six membered heterocycle[16] *viz.* 1,2,3-benzoxathiazine-2,2-dioxides (11). The reaction of *o*-hydroxy acid chlorides, in the presence of triethylamine, yields 2,4-dioxo-3,4-dihydro-2H-benzo-[*e*]-1,3-oxazines[17] (12). The same compound 12 was prepared by another route[18] as depicted in scheme I.1.4.

SCHEME I.1.4



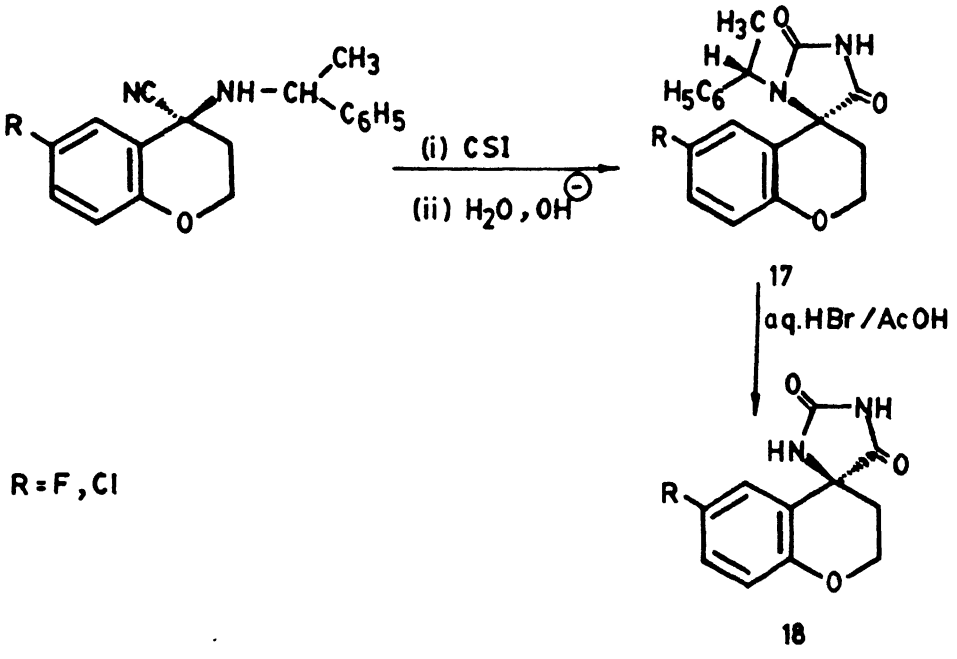
The facile reaction of CSI with amines has been exploited in the synthesis of some heterocyclic compounds. The reaction of 2-aminopyridines and 2-aminopyrazines[19] with CSI yield an intermediate which undergoes smooth cyclization in the presence of N,N-diisopropylethylamine to give thiatriazine **13**. Similarly, 2-amino-4,5-dihydro-1,3-thiazole and some isothioureas[20] react with CSI, followed by reaction with tertiary base to give substituted thiatriazines **14**, **15**. A novel and selective synthesis of 2H-1,2,4-benzothiadiazin-3(4H)-one-1,1-dioxides[21] (**16**) has been achieved by the reaction of CSI with anilines, followed by Friedel-Crafts cyclization as shown in Scheme I.1.5.

SCHEME I.1.5



Optically active spirohydantoins[22] **17,18** were prepared by the reaction of CSI with sterically hindered aminonitriles followed by hydrolysis (Scheme I.1.6).

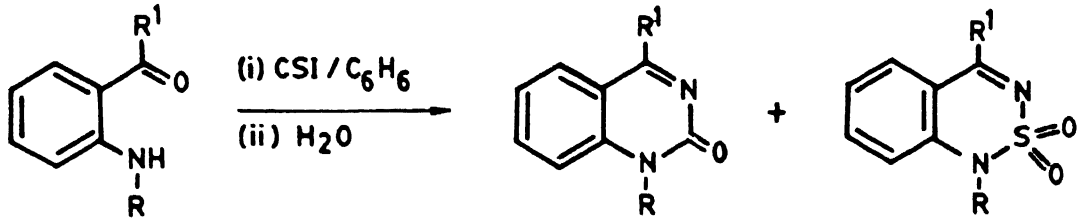
SCHEME I.1.6



2-Aminoacetophenones and 2-aminobenzophenones[23] undergo heterocyclization with CSI to produce 2H-quinazolines (**19**) as major products and thiaquinazoline-1,1-dioxides (**20**) as minor products. A similar reaction of methylanthranilate[18] with CSI produced 2,4-quinazolindione (**21**) (Scheme I.1.7). Some other examples of heterocycles **22,23** which are prepared by the cyclization of various amino compounds[24,25] with CSI are shown in scheme I.1.8.

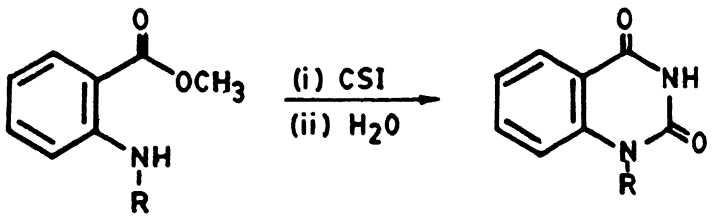
CSI undergoes cycloaddition with 2-alkyloxazolines and thiazolines[26] to yield the new class of fused heterocycles (**24**). However, 2-aryloxazolines and thiazolines under similar experimental conditions, gave the corresponding 2-(*o*-phenylsulfonamido)-oxazolines and thiazolines derivatives **25** (Scheme I.1.9).

SCHEME 1.1.7



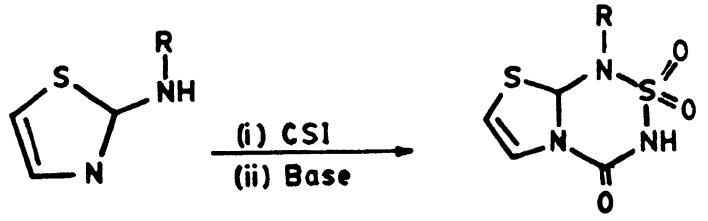
19 20

R = H , CH_3
R^1 = CH_3 , aryl

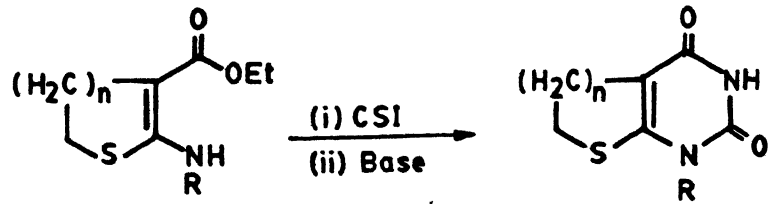


21

SCHEME 1.1.8

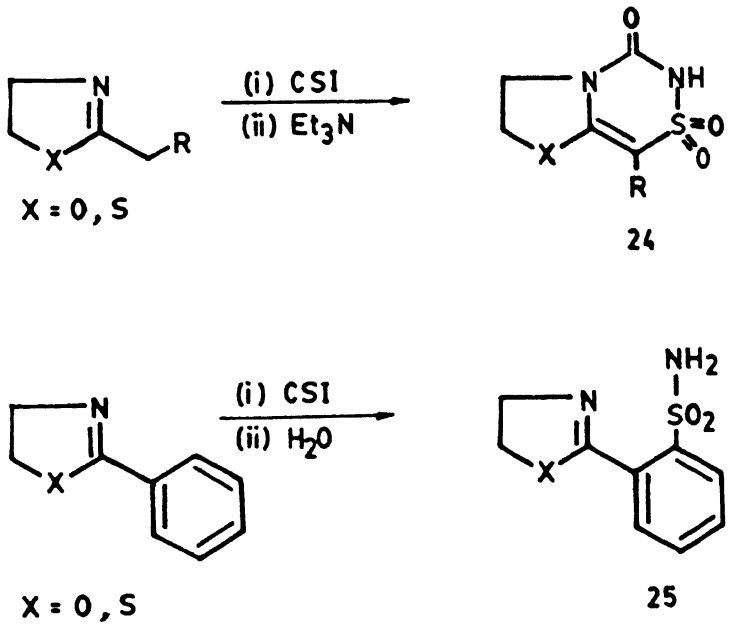


22



23

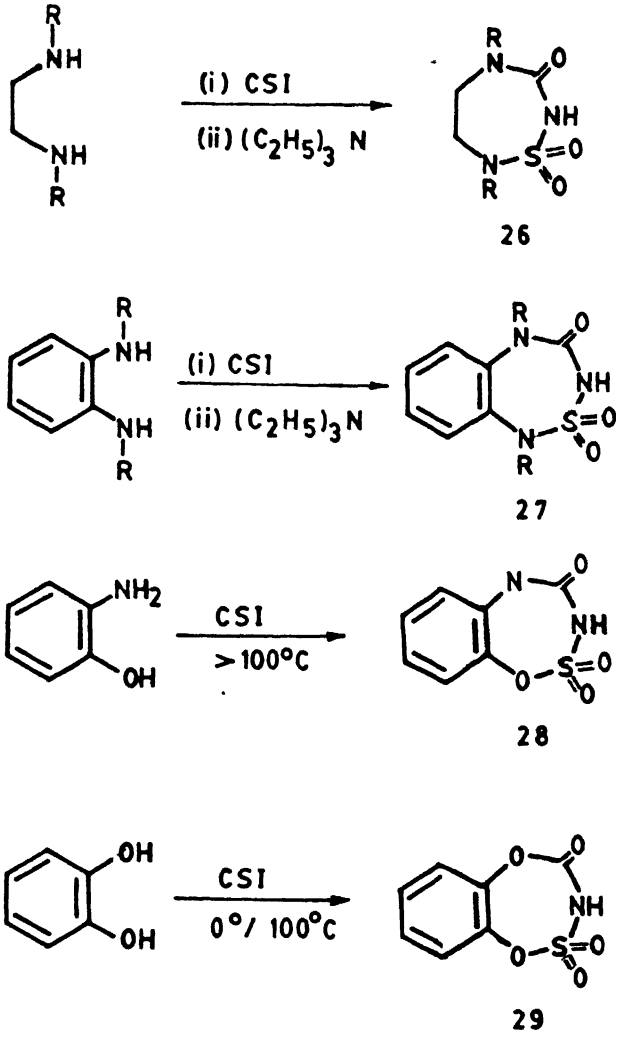
SCHEME 1.1.9



The reaction of 1,2-diamines[27] with CSI give 4,5,6,7-tetrahydro-1,2,4,7-thiatriazepin-3(2H)-one-1,1-dioxides (26). Similarly, *o*-phenylenediamines[27] give 1,3-dihydro-2,1,3,5-benzothiatriazepin-4-(5H)-one-2,2-dioxide (27). Addition of CSI to 2-aminophenols[18] at higher temperature affords (3H)-1,2,3,5-benzoxathiadiazepin-2,2-dioxide-4(5H)-ones (28). Catechols[28] at $0^{o}/100^{o}C$ undergo heterocyclization with CSI to produce another class of seven membered heterocycles, *viz.*, 1,5,2,3(3H)-benzodioxathiazepin-2,2-dioxo-4-ones (29) (Scheme I.1.10).

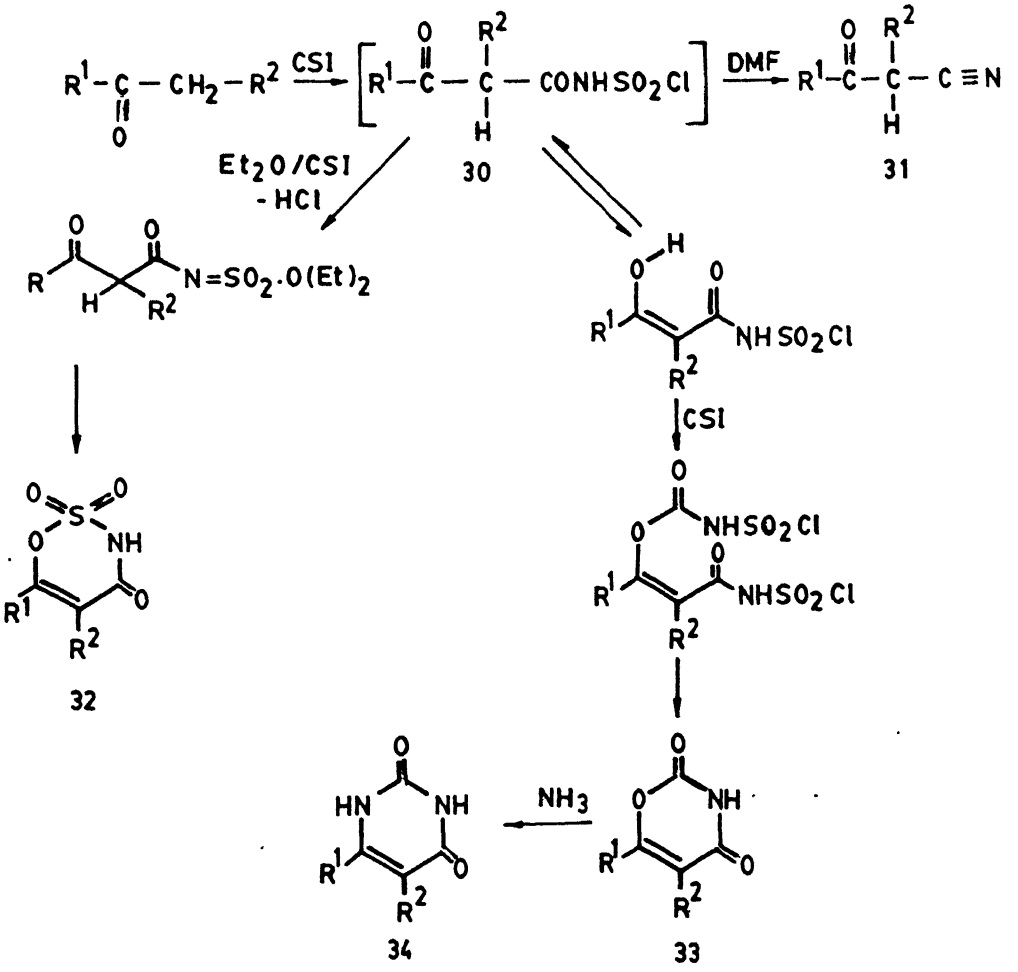
CSI undergoes electrophilic addition to enolizable ketones yielding N-chlorosulfonyl-β-ketocarboximide[29,30] (30). These are not isolable but are used as intermediates in the synthesis of many important compounds. For example, β-ketonitriles[31] (31) can be prepared from the intermediate 30 on treatment with DMF.

SCHEME I-1-10



Rasmussen and Hassner[30] reported for the first time the electrophilic addition of CSI to simple ketones, which provides a facile synthesis of six membered heterocycles, *viz.*, 1,2,3-oxathiazin-4(3H)-2,2-dioxides (32), when ether was used as solvent. 5,6-Disubstituted uracils[32] (34) can be prepared by the reaction of CSI with ketones. The final products distribution is dependent upon the effects of solvent, substituents and concentration[30,32] (Scheme I.1.11).

SCHEME 1.1.11

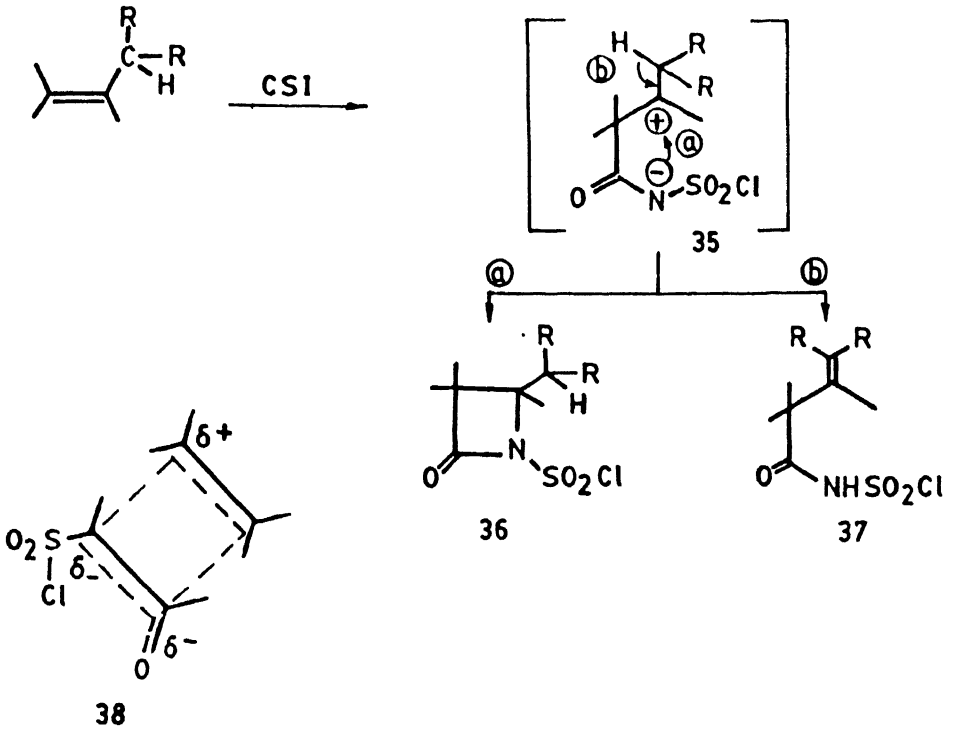


I.2 CYCLOADDITION REACTIONS

I.2.1 Reaction with carbon-carbon multiple bonds

The ability of CSI to undergo cycloaddition to carbon-carbon multiple bond adds another dimension to its usefulness. Thus, the [2+2] cycloaddition[33-38] of CSI to a wide variety of olefins is reported to produce β-lactams, according to the scheme (I.2.1). From the synthetic point of view these reactions are of importance, because, the β-lactams are the basic units of penicillin type-drugs

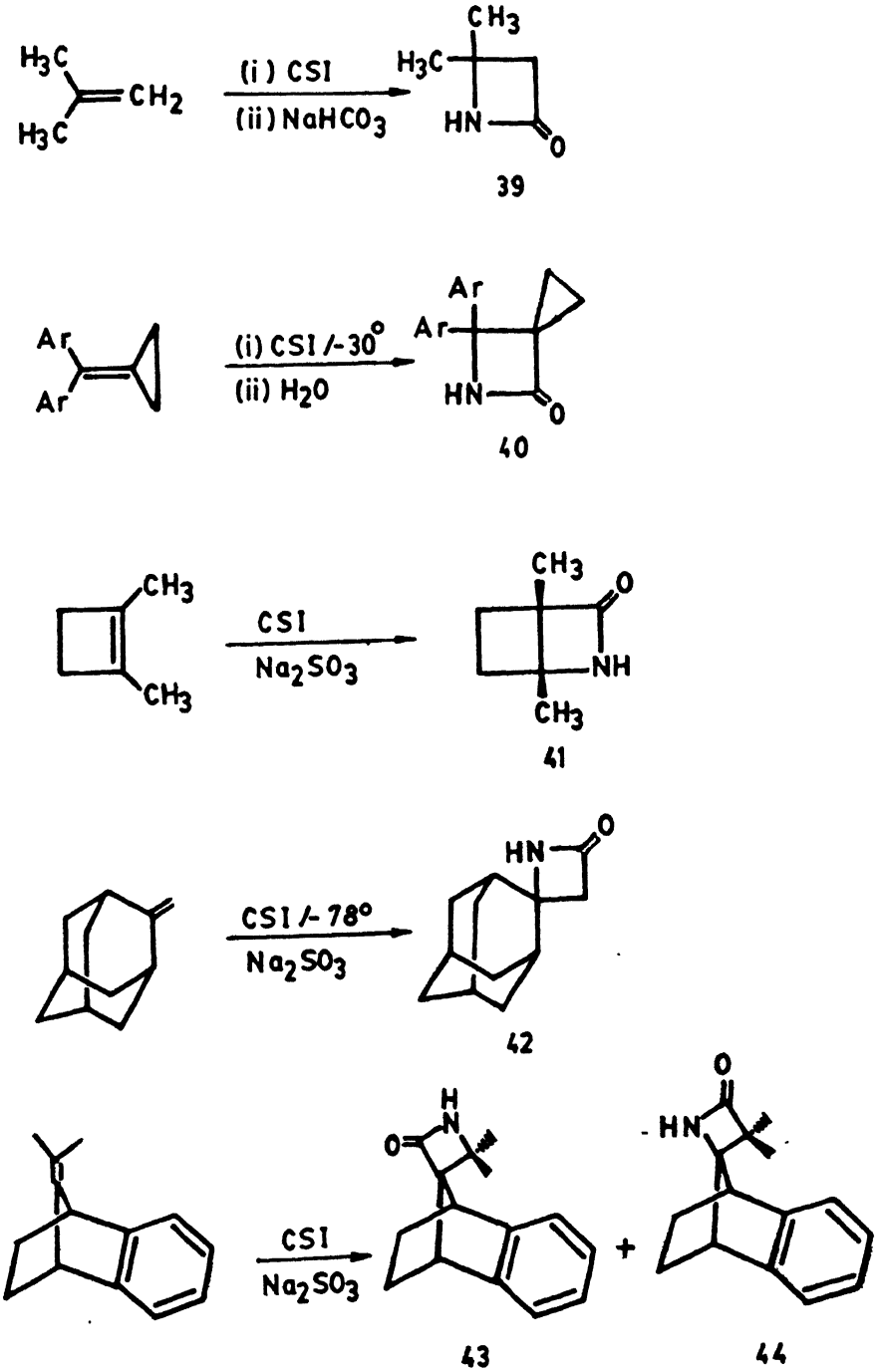
SCHEME I·2·1



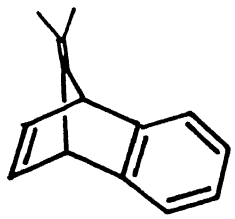
and this is the simplest way to achieve the synthesis of β-lactams by utilizing CSI. Mono-olefins undergo reaction with CSI forming 1:1 cyclic (β-lactam) and linear adducts[36] *viz.*, N-chloro-sulfonyl-β-lactams (36) and N-chlorosulfonylcarboxamides (37) respectively as shown in scheme I.2.1. Adducts of type 37, usually accompany the formation of β-lactams (36). Their proportion in the product mixture appears to be the function of pattern and the type of substitution on olefins. Graf[36], originally proposed a two-step mechanism for this reaction, according to which the initially formed adduct is the 1,4-dipolar species (35), which undergoes ring closure to give β-lactam (36) and the unsaturated amide (37) *via* a proton

shift. Moriconi and Meyer[38] on the other hand proposed a concerted thermally allowed [π^2s + π^2a][37] cycloaddition probably initiated by a π-complex formation and proceeding through a polar transition state **38**. The cycloaddition is found to highly stereo- and regiospecific. In other words, the *cis*-adduct is always formed and the addition

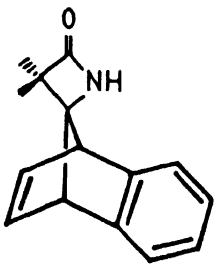
SCHEME 1-2-2



SCHEME 1·2·2 Contd

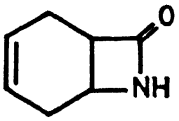


CSI
H_2O

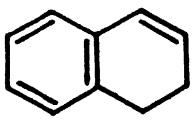


45

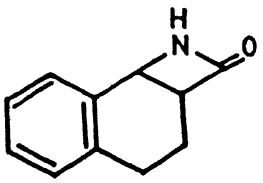
CSI
H_2O



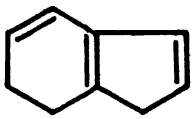
46



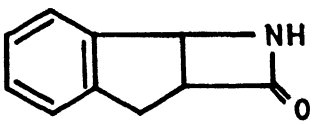
CSI
Na_2SO_3



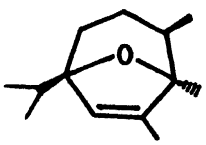
47



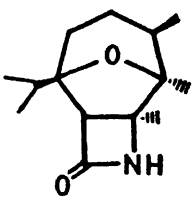
CSI
Na_2SO_3



48



CSI
H_2O

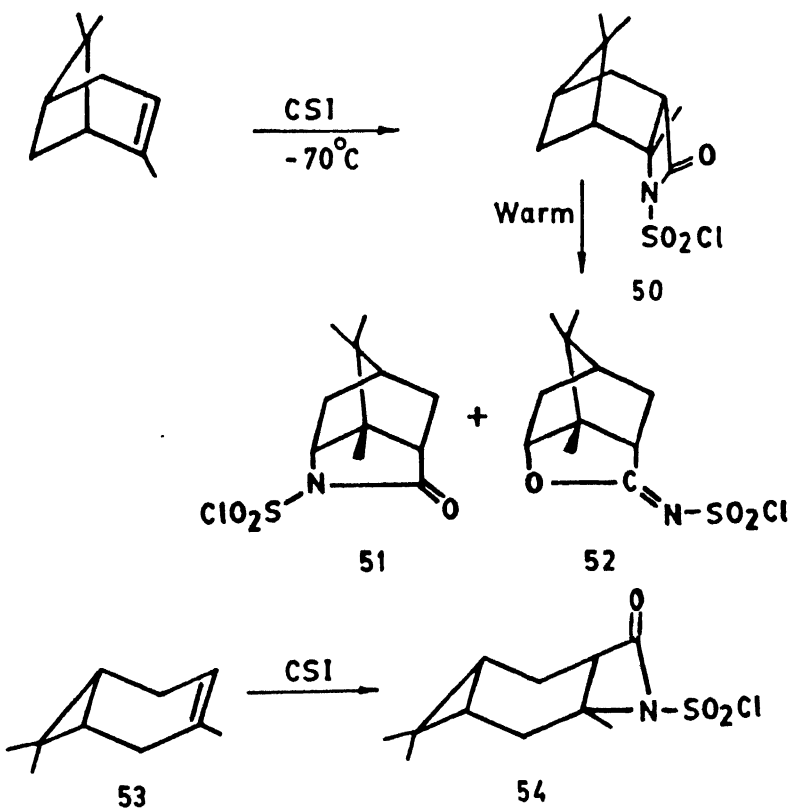


49

takes place in such a way that the most stable carbocation would be generated. The examples quoted in scheme I.2.2 highlight the usefulness of CSI for the preparation of a variety of β-lactams[39-46] **39-49**.

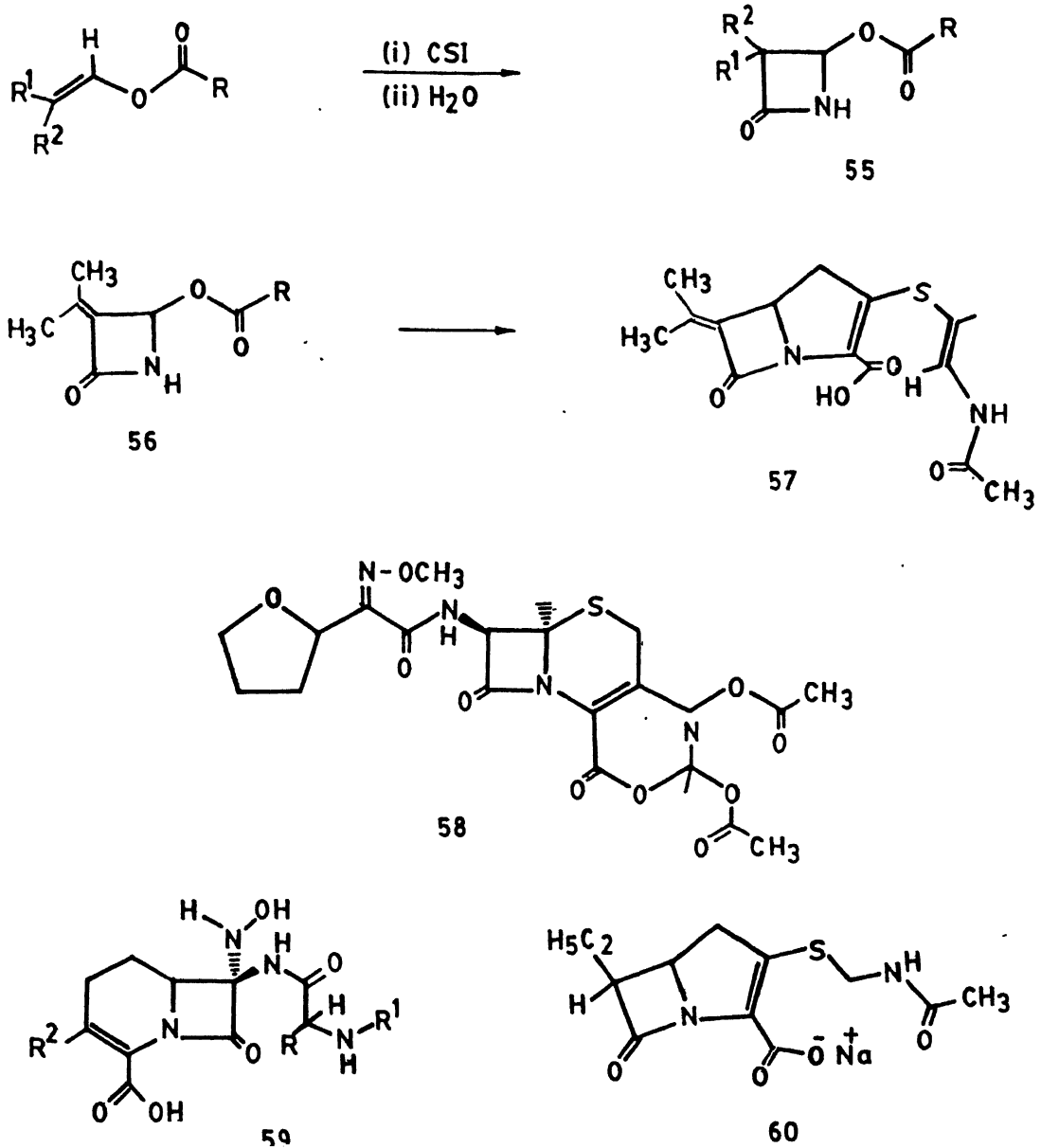
The cycloaddition of CSI to mono-terpene olefins[47-49] gave the unrearranged products i.e., N-chlorosulfonyl-β-lactams, at low temperature. On warming these β-lactams get transformed to rearranged products. Cycloaddition reaction of CSI with α-pinene at -70°C produces, β-lactam **50**, which rearranges on warming to **51** and **52**. But the reaction of CSI with Δ^3-carene produces the stable β-lactam **54**. This inconsistency in the results obtained with mono-terpene olefins appear to be due to slight variations in the reaction conditions and mode of work-up (Scheme I.2.3).

SCHEME I.2.3



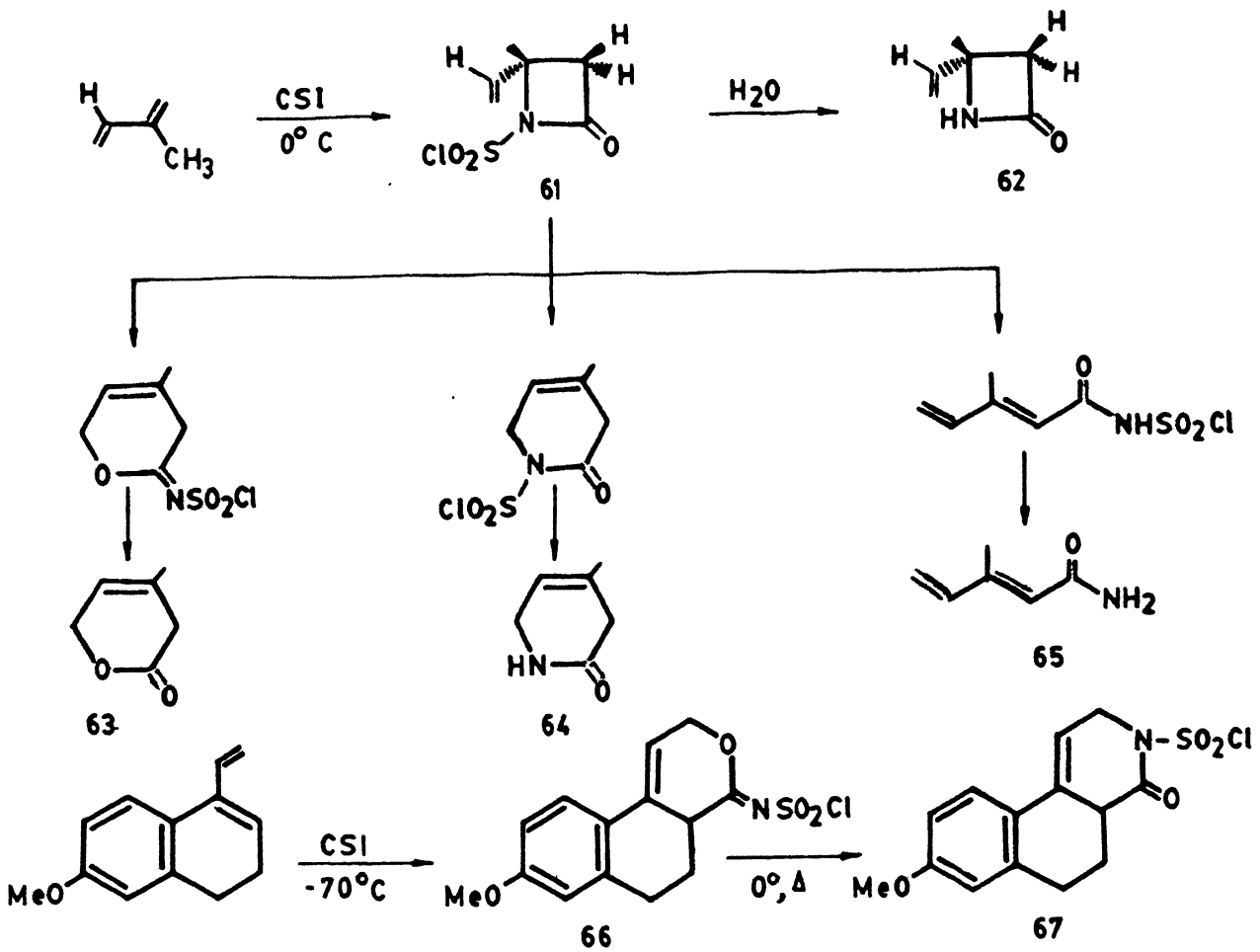
CSI undergoes [2+2] cycloaddition with heterosubstituted olefins such as vinyl esters[50], leading to the corresponding azetidinones **55** upon hydrolysis. These azetidinones are important building blocks for the total synthesis of many antibiotics[51-56] *viz.*, penicillin, cephalosporin and oxacephem class of compounds. In all these synthesis, an important step involves the β-lactam ring formation. Some of the examples **56-60** bearing β-lactam ring[57-60] are shown in scheme I.2.4.

SCHEME I.2.4



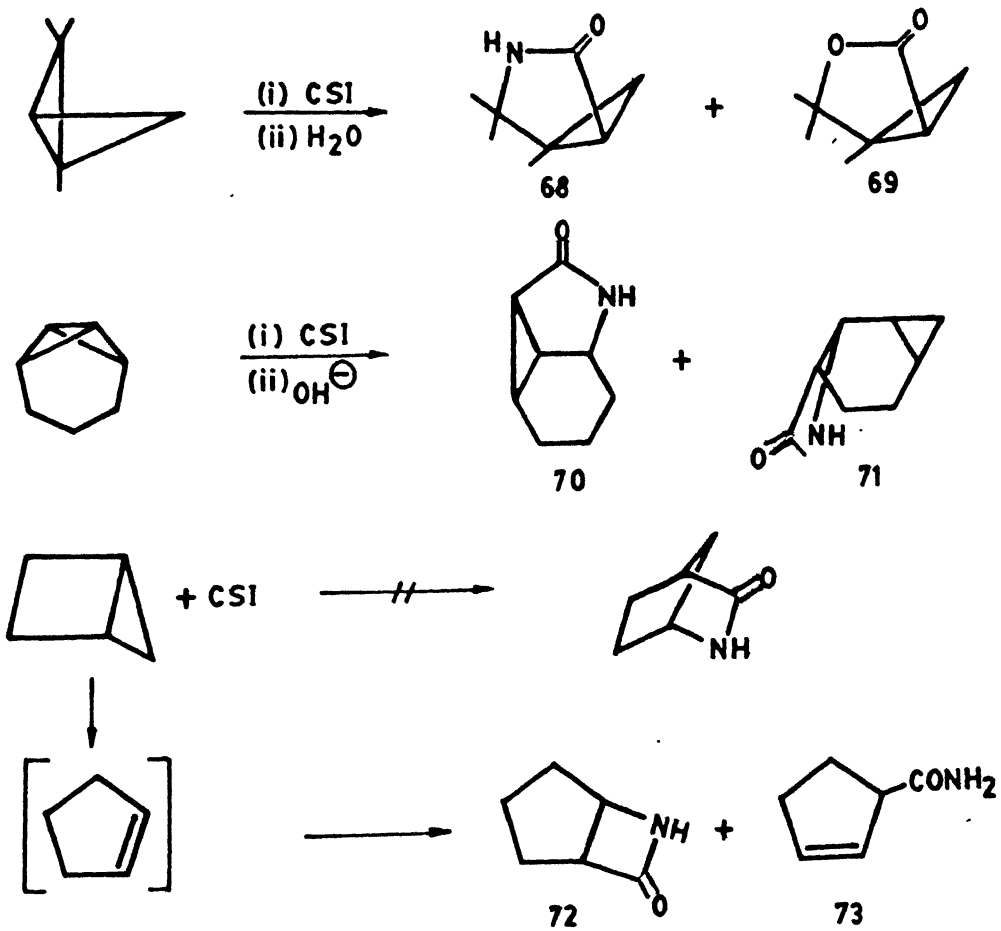
The reaction of CSI with conjugated 1,3 dienes[38,61] and trienes are well documented in literature. These undergo 1,2- as well as 1,4-addition reactions with CSI. The initially formed β-lactam **61** undergoes rearrangement to give 1,4-addition products **63**, **64** and unsaturated amide **65**. Addition of CSI to vinyl dihydronaphthalene[62] at -70°C produces iminolactone **66**, which on warming rearranges to lactam **67** (Scheme I.2.5).

SCHEME I.2.5



Strained carbon-carbon single bonds of certain bicyclic hydrocarbons undergo formal cycloaddition reactions with chlorosulfonyl isocyanate. This is mainly due to the high degree of *p*-character[63] in their σ-bonds. The reactions are similar to those of olefins and the products obtained are often novel heterocycles which are difficult to prepare by other methods. Some examples of heterocycles **68-72** which are obtained by the reactions of bi- and tricyclic hydrocarbons[63-65] are shown in scheme I.2.6.

SCHEME I·2·6



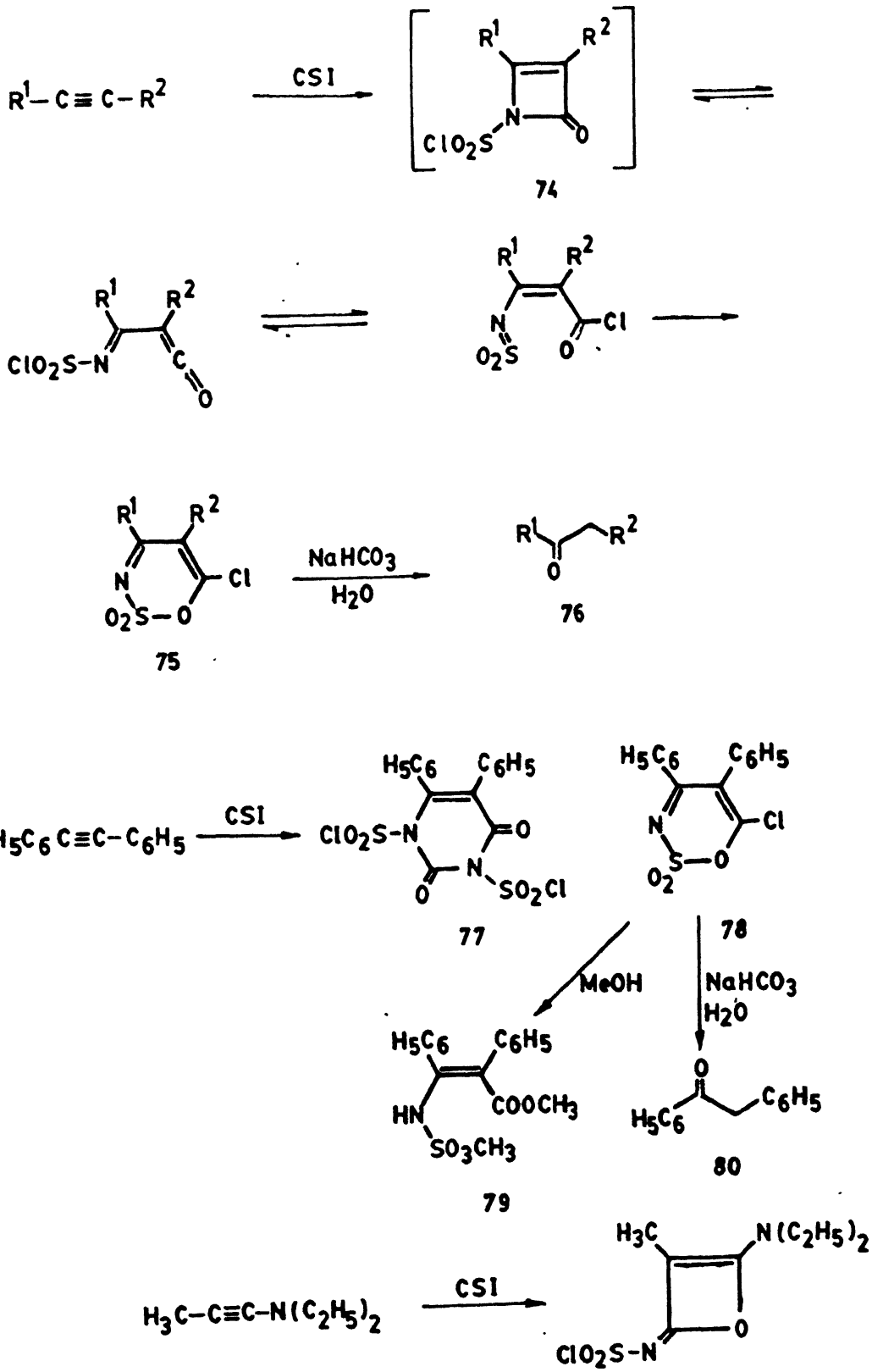
CSI reacts with acetylenes to produce six-membered heterocyclic compounds[66] **75**. The initially formed intermediate **74** undergoes rearrangement to 1,2,3-oxathiazine-2,2-dioxide **75**. The hydrolysis of **75** affords a ketone **76**. Diphenylacetylene[66] however, reacts in a different way to produce 1,3-*bis*-(chlorosulfonyl)-5,6-diphenyl-uracils (**77**) and oxathiazine-2,2-dioxide (**78**). The compounds **79** and **80** can be visualized to be formed from the common intermediate **78**. In some cases (R^2 = $N(C_2H_5)_2$)[66] a [2+2] cycloadducts **81** were isolated. In this example, the cycloaddition occurs across the C=O bond of CSI (Scheme I.2.7).

With simple allenes,[33,67-69] CSI adds predominantly to the central carbon atom of the allenic system resulting in the formation of stable tertiary carbonium ion **82**. This species attains additional stabilization as an allylic cation. Thus, 3-methyl-1,2-butadiene on reaction with CSI gives a β-lactam **83** and an unsaturated amide **84**. β-lactams generally predominate. Cyclopropylidene derivatives react with CSI to produce "reversed" regioisomers **85**.

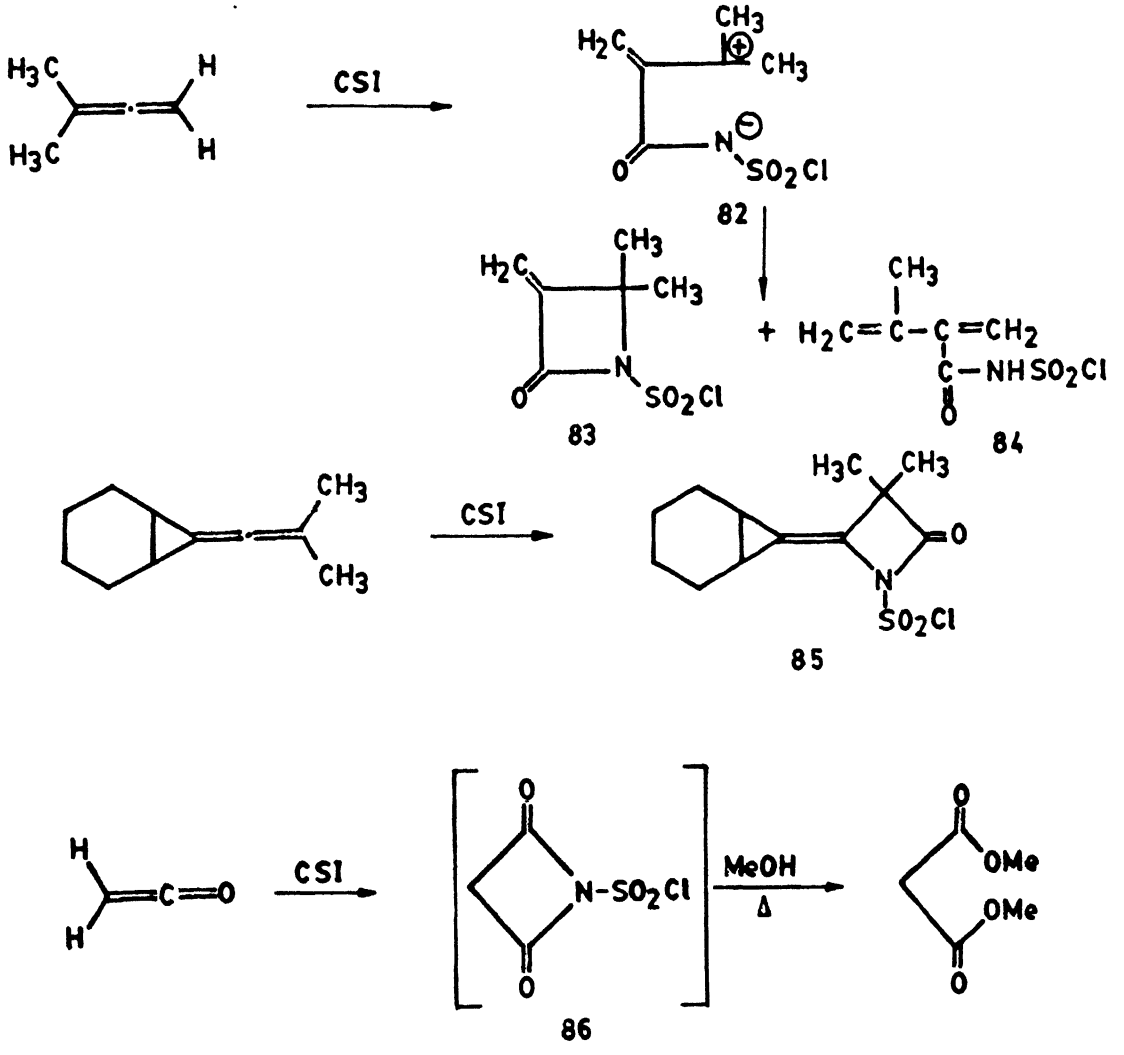
Mundlos and Graf have reported[70] that the reaction of unsubstituted ketene with CSI, at low temperature, yields an unstable imide **86** which on heating with methanol is readily transformed into dimethylmalonate. Scheme I.2.8 illustrates the reactions of allenes and ketenes with CSI.

Besides [2+2] and [4+2] higher order cycloaddition reactions of CSI with unsaturated compounds are also known. A [8+2][71] cycloaddition was observed with 1-methoxy-3-methylindene (**87**) and led to the formation of lactams **88** and **89**. Ferber *et al.*,[72] reported a [8+2] cycloaddition reaction of 7-alkylidene cycloocta-1,3,5-triene (**90**) with CSI to produce **91** (Scheme I.2.9).

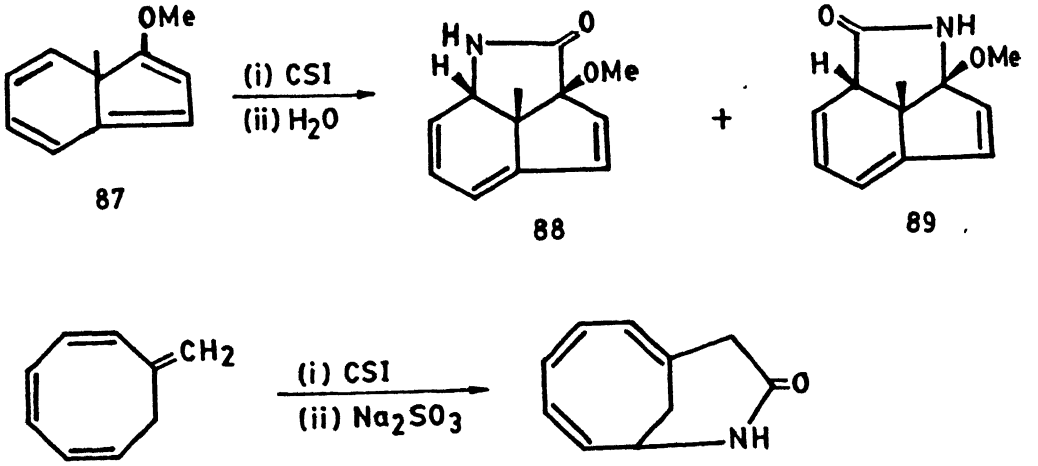
SCHEME 1·2·7


R1–C≡C–R2
CSI
ClO2S
74
ClO2S–N
Cl
O2S
75
NaHCO3
H2O
76
H5C6C≡C–C6H5
C6H5
SO2Cl
77
78
MeOH
NaHCO3
H2O
HN
COOCH3
SO3CH3
79
80
H3C–C≡C–N(C2H5)2
N(C2H5)2

SCHEME I·2·8



SCHEME I·2·9



I.2.2 Reaction with carbonyl compounds

The reaction of CSI with non-enolizable carbonyl compounds is a useful method for the synthesis of N-chlorosulfonylimine.[29] Aldelhydes react with CSI at room temperature to form N-chlorosulfonyl azomethene (93) and carbon dioxide. The formation of 93 may be visualized to take place through the intermediate[29]92 or a 1,4-dipolar species 94. However, at low temperature it has been observed that CSI reacts with another molecule of aldehyde, resulting in the formation of dioxazinone[29] 95.

Non-enolizable aromatic ketones react with CSI to form benzoisothiazole dioxides[29] (97) *via* the intermediate azomethine 96. Benzopinacolones react with CSI to produce benzoisothiazole dioxides[73,74] 98. Hydrolysis of 98 yields the corresponding sulfonamide 99.

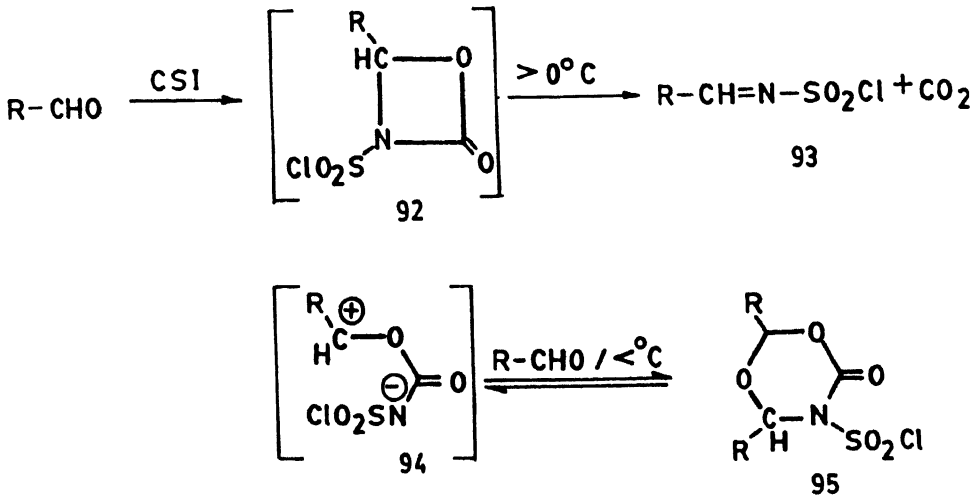
α,β-unsaturated ketones[29] *viz.*, chalcones[73] undergo [4+2] cycloaddition with CSI to produce 3,4-dihydro-1,3-oxazine-2-ones (101) in a good yield. On the other hand phorone reacts with CSI in the ratio of 1:2 to give a [2+2+2][29] cycloadduct 102.

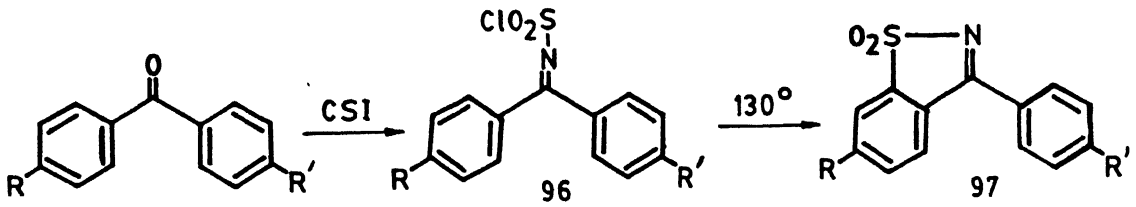
The reaction of chlorosulfonyl isocyanate with aryl methylene malonaldehydes are reported[75] to afford the fused 1,3-oxazin-2-one derivatives (103). Various reactions of carbonyl compounds are shown in scheme I.2.10.

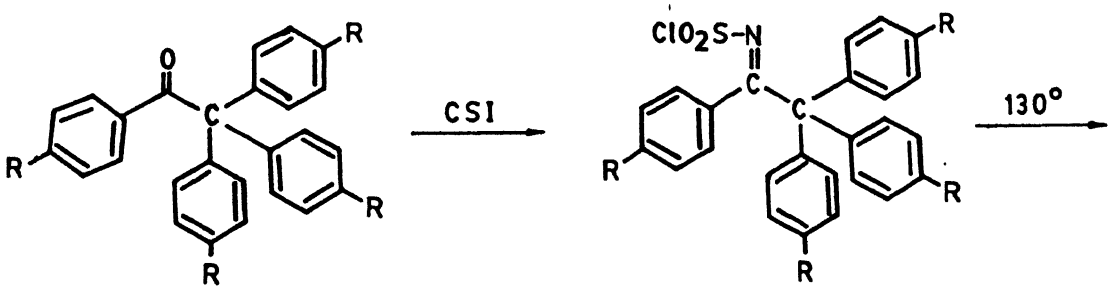
I.2.3 Reaction with carbon-nitrogen double bonds

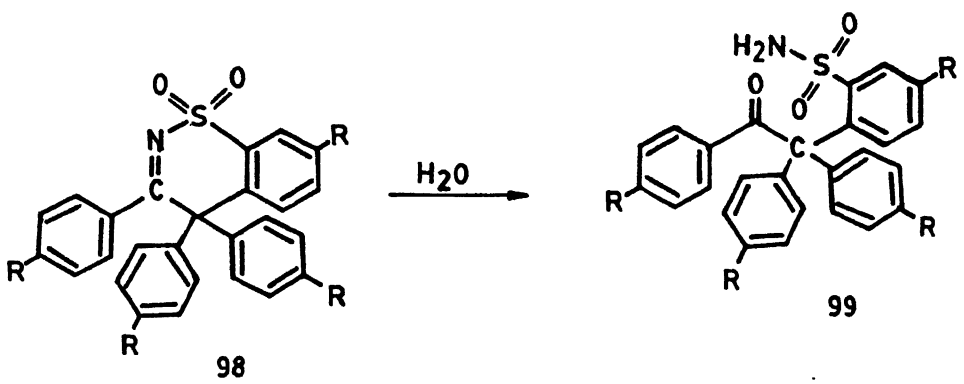
CSI reacts with anils and azines in the ratio of 2:1 and gives triaziniediones. Thus, CSI reacts with azomethines to produce 1,3,5-triaziniediones[76,77] (104). Azines react with two mole equivalents of CSI, giving rise to a *bis*-heterocyclic compound 106. Slow addition of CSI to the diimides[76]produces diazetidinone 109.

SCHEME I·2·10

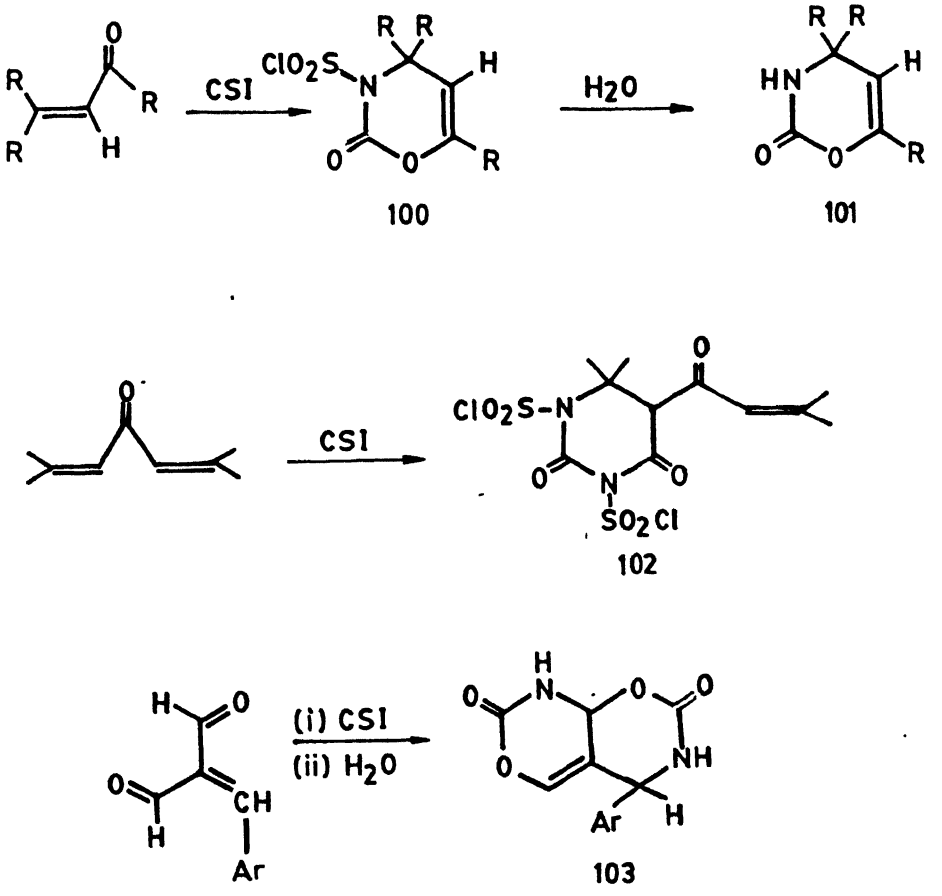

R-CHO
CSI
R
HC
O
N
ClO_2S
O
92
>0°C
R-CH=N-SO_2Cl + CO_2
93
R-CHO / <°C
94
95
SO_2Cl


CSI
ClO_2S
N
96
130°
O_2S
97


CSI
ClO_2S-N
130°

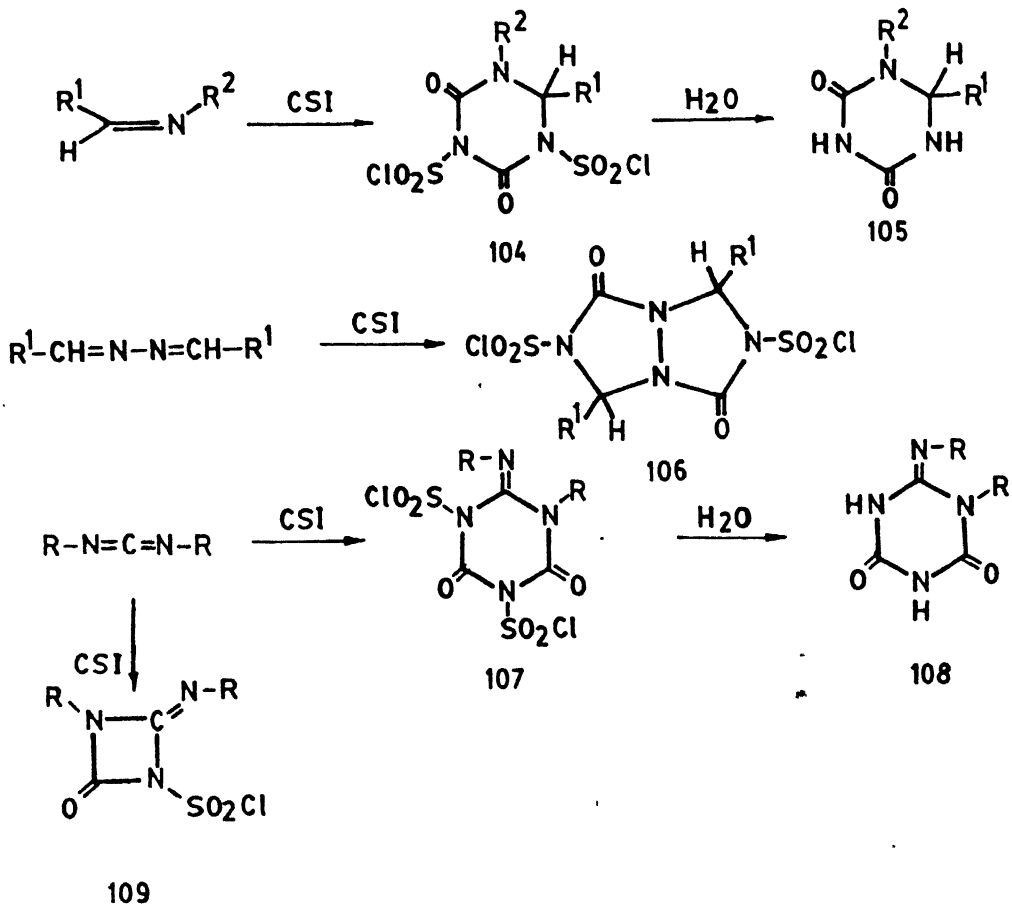

H_2O
H_2N
98
99

SCHEME 1·2·10 Contd.



While with inverse addition of CSI, produces a 2:1 CSI-diimide adduct, triazindioximine 107. This adduct, 107 on hydrolysis gives 108 (Scheme I.2.11).

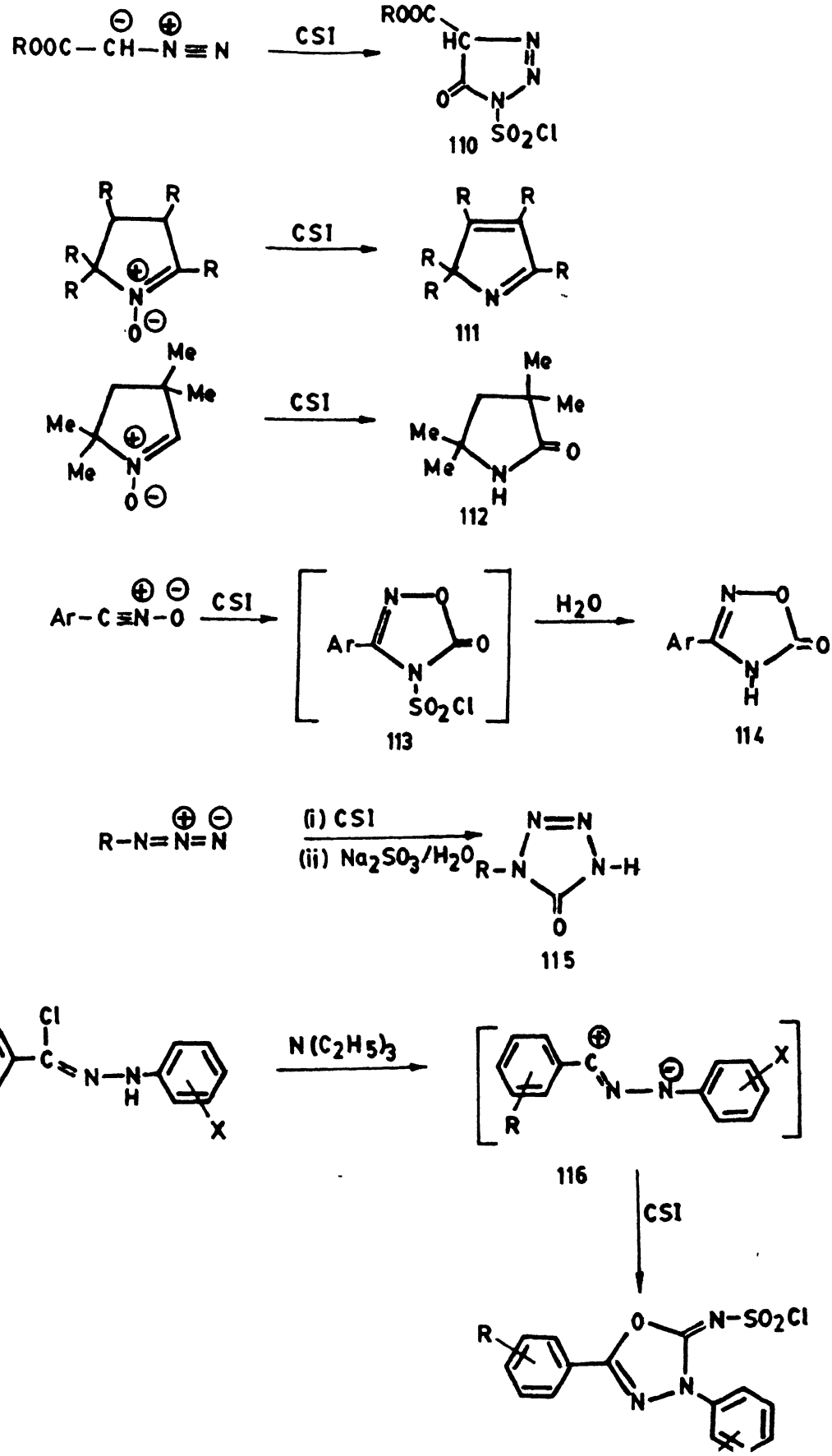
SCHEME I·2·11



I.2.4 Reaction with 1,3-Dipolar Species

CSI undergoes cycloaddition with variety of 1,3-dipolar species *viz.*, nitrones, aryl nitrile oxides, alkylazides, nitrilimines (Scheme I.2.12). In most of the cases the addition of the 1,3-dipolar species occur across the C=N moiety of CSI. Diazoacetic esters[3] react with CSI across the C=N bond to produce 1-chlorosulfonyl-5-oxo-2-triazolin-4-carboxylic acid derivatives (**110**). Joseph and Dhar[78] reported the conversion of 3,4-dihydro--2H-pyrrole-1-oxides to the corresponding 2H-pyrroles (**111**) and 3,4-dihydro-2,2,4,4-tetramethylpyrrole-1-oxides to 3,3,5,5-tetra-

SCHEME 1·2·12


ROOC—CH—N≡N
CSI
ROOC
HC
N
N
O
N
SO2Cl
110
R
R
R
R
R
N
O
CSI
R
R
R
R
R
N
111
Me
Me
Me
Me
N
O
CSI
Me
Me
Me
Me
N
H
O
112
Ar—C≡N—O
CSI
N
O
Ar
O
N
SO2Cl
113
H2O
N
O
Ar
O
N
H
114
R—N=N=N
(i) CSI
(ii) Na2SO3/H2O
N=N
R—N
N—H
O
115
R
Cl
C
N—N
H
X
N(C2H5)3
C
N
N
X
R
116
CSI
R
O
N—SO2Cl
N
N

CSI reacts with aryl nitrile oxides[79] to furnish a highly stereoselctive unstable cycloadduct **113**, which on hydrolysis yields the 3-aryl-1,2,4-oxadiazolin-5-one (**114**). Tetrazolones[76,80] **115** are obtained by the reaction of CSI with alkyl azides. Diarylnitrilimines[81] (**116**), generated *in situ*, react across the C=O group of CSI at 5-10°C leading to the exclusive formation of 2-chlorosulfonylimino-3,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles (**117**).

1.3 REACTION WITH SMALL RING HETEROCYCLES

1.3.1 Reaction with oxiranes

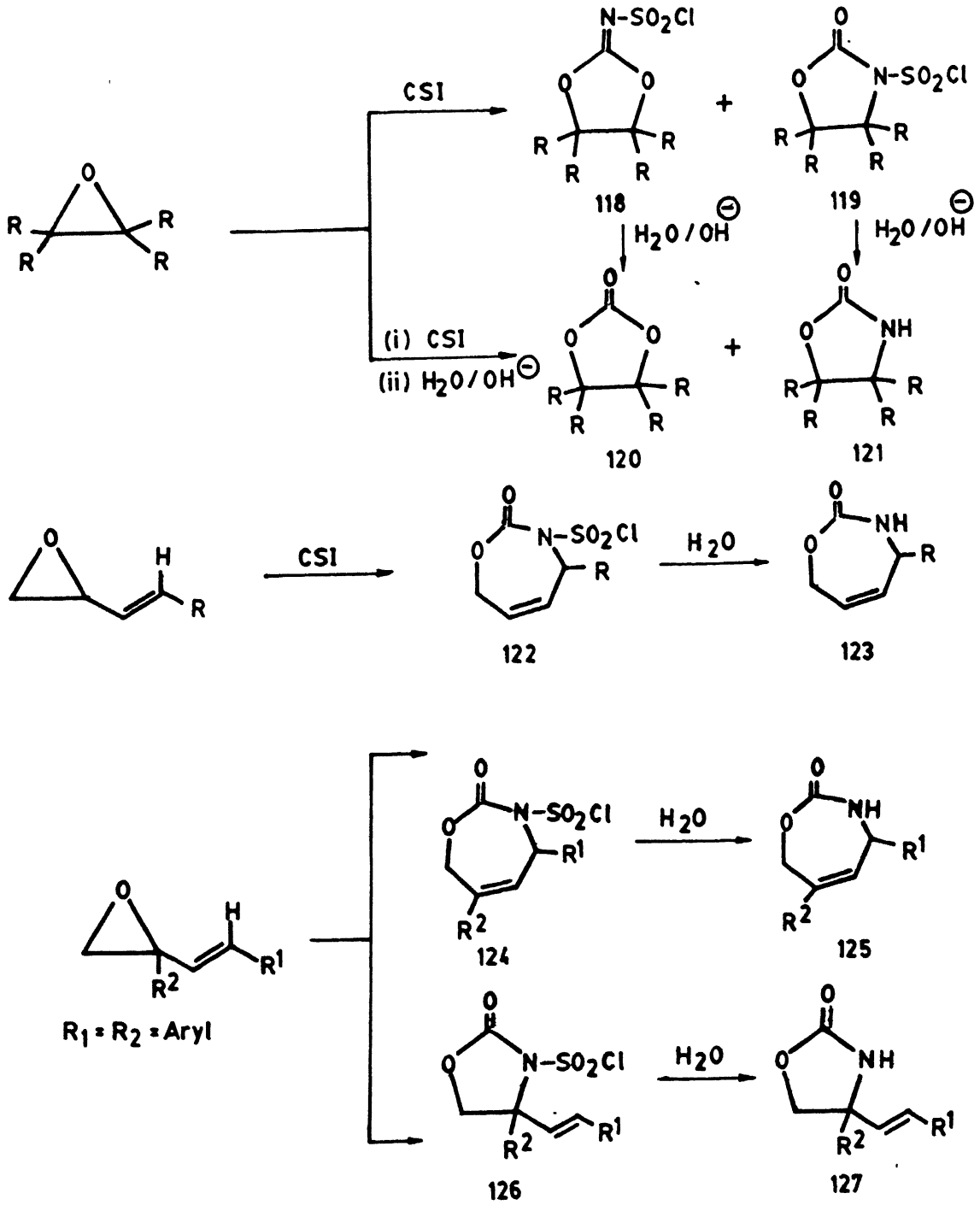
Chlorosulfonyl isocyanate reacts with oxiranes[82] to produce N-chlorosulfonylimino-1,3-dioxalanes (**118**) and N-chlorosulfonyl 1,3-oxazolidin-2-ones (**119**). The initially formed heterocycles undergo smooth hydrolysis to the corresponding 1,3-dioxalane-2-ones (**120**) and 1,3-oxazolidin-2-ones (**121**). The reaction is both regio- and stereospecific.

Recently, Daniel[83] *et al.*, reported the reaction of some vinyloxiranes with CSI. Thus, CSI reacts with vinyloxiranes to give the seven membered heterocycle oxazepinone derivatives (**122-125**) and vinyl substituted oxazolidine derivatives (**126,127**) in good yields. Reactions of oxiranes and vinyloxiranes with CSI are shown in Scheme I.3.1.

1.3.2 Reaction with Aziridines and Azirines

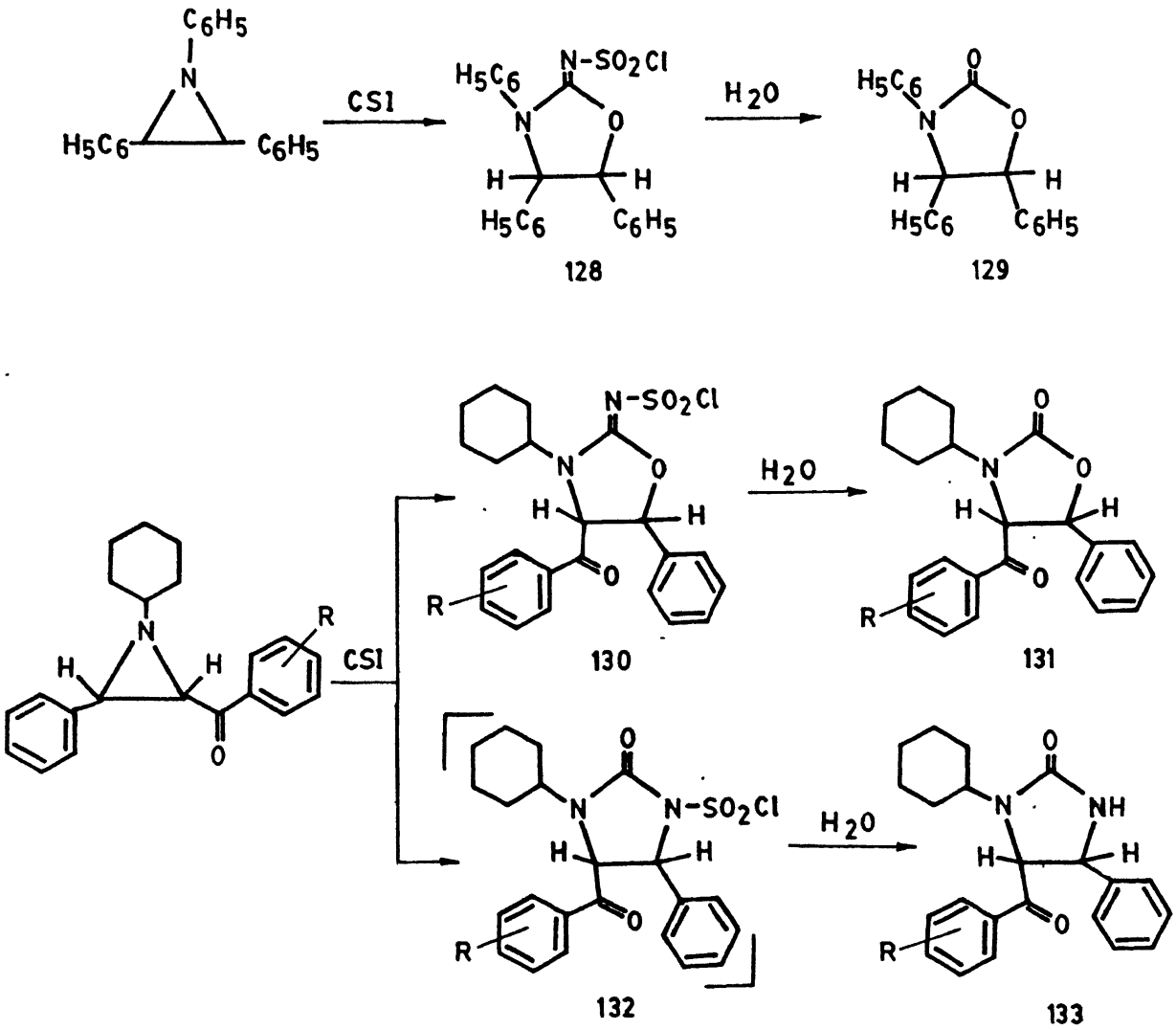
Aziridines[84], the three membered nitrogen containing heterocycles, are reported to react with CSI in a manner analogous to that of oxiranes (cf. I.3.1). Thus, *cis*-1,2,3-Triphenyl aziridine on reaction with CSI produced the N-chlorosulfonylimino-1,3-oxazolidine **128** which undergoes hydrolysis to the corresponding oxazolidin-2-one

SCHEME 1·3·1


CSI
N-SO2Cl
118
119
H2O/OH⊖
(i) CSI
(ii) H2O/OH⊖
120
121
NH
CSI
H2O
122
123
R1 = R2 = Aryl
124
125
126
127

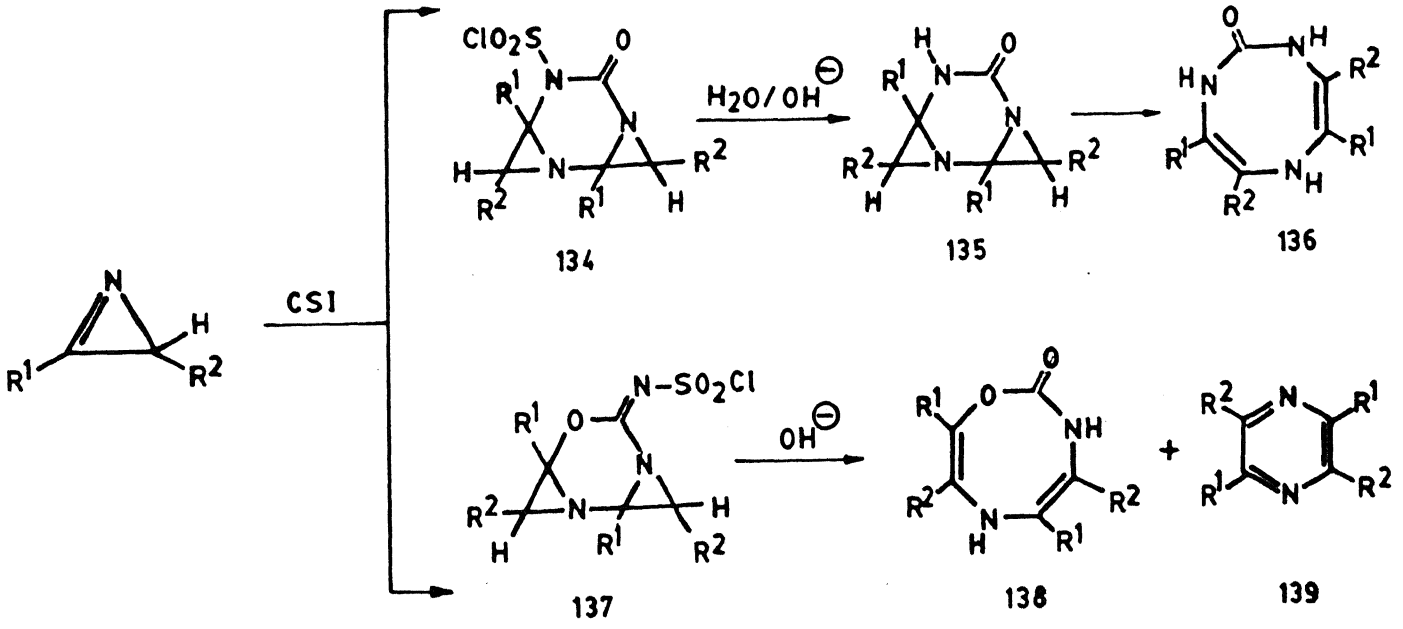
129. Substituted *cis*-1-cyclohexyl-2-aryol-3-phenyl aziridines react readily with CSI to yield 2-N-chlorosulfonylimino-1,3-oxazolidine derivatives 130 as major product. The formation of other isomeric product *viz.*, N-chlorosulfonyl-1,3-imidazolidin-2-one 132 has been proved by spectroscopic and chemical methods by isolating its corresponding hydrolysed product, oxazolidin-2-one 133 (Scheme I.3.2).

SCHEME I.3.2



CSI reacts with 2 mole equivalents of 2H-azirines[85] at -78°C to produce N-chlorosulfonyl-[3,4]-[5,6]-dimethylene-4,6-diphenyl-1,3,5-triazin-2-ones(134), N-chlorosulfonylimino [3,4] [5,6] dimethylene-4,6-diphenyl-1,3,5-oxadiazenes (137) and 2,5-diaryl pyrazines (139). These tricyclic aziridine derivatives are convertible, on hydrolysis, to the corresponding eight membered azocinones 136 and oxazocinones 138. A [2+2+2] cycloadditive path has been proposed[95] for the above reaction. Thus, CSI adds across the two reactive π bonds of 2H-azirines in two different ways. The C=N bond addition leads to the formation of 136, while C=O addition leads to 138 (Scheme I.3.3).

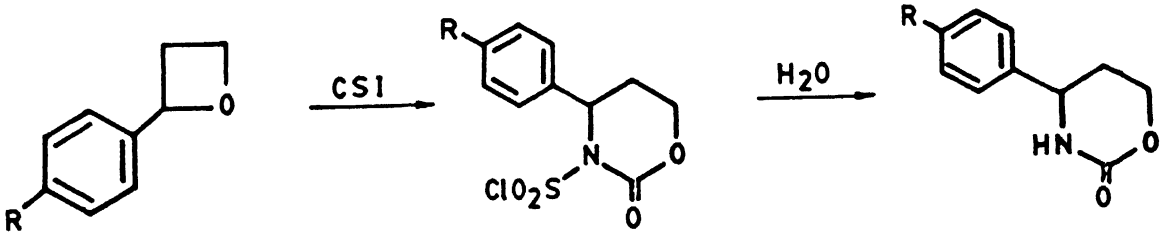
SCHEME I.3.3



I.3.3 Reaction with Oxetanes

Oxetanes[86], the four membered oxygen containing heterocycles, undergo ring opening with CSI to give six membered heterocyclic systems. Thus, 2-aryl—oxetanes on reaction with CSI yield N-chlorosulfonyl-4-aryl-1,3-oxazin-2-ones (140). Hydrolysis of 140 yield the 4-aryl-1,3-oxazin-2-ones (141), as depicted in scheme I.3.4.

SCHEME I.3.4



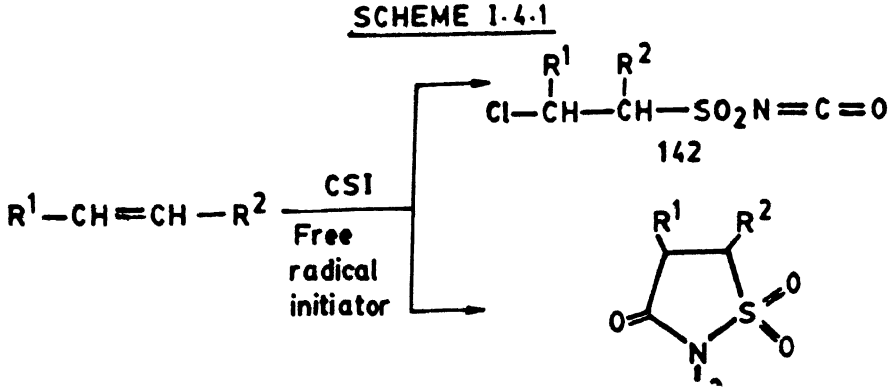
R = H, Cl 140 141

1.4 MISCELLANEOUS REACTIONS

1.4.1 Free radical reactions

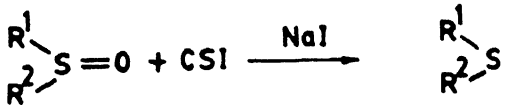
In presence of free radical initiators (*viz.*, peroxides or uv light) CSI reacts with olefins to produce 2-chloroalkane sulfonyl isocyanates[87] (142). By changing the reaction conditions the course of the reaction is changed considerably and 2-(2-chloroalkyl)-3-oxo-isothiazolidine-1,1-dioxides (143) are produced as shown in Scheme I.4.1.

SCHEME I.4.1



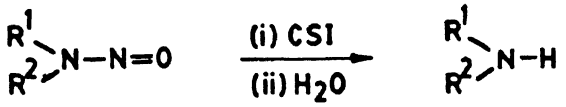
1.4.2 Reaction with sulfoxides

Alkyl and aryl sulfoxides[88] are reduced to the corresponding sulfides in excellent yields by their reaction with CSI and sodium iodide.



1.4.3 Reaction with nitrosoamines

The nitrosoamines[89] have been found to react with chlorosulfonyl isocyanate in a facile manner to yield a product which, after hydrolysis, gives the amines in good yield. Thus, CSI has been exploited for effecting the denitrosation of nitroso compounds.



1.4.4 CSI as dehydrating agent

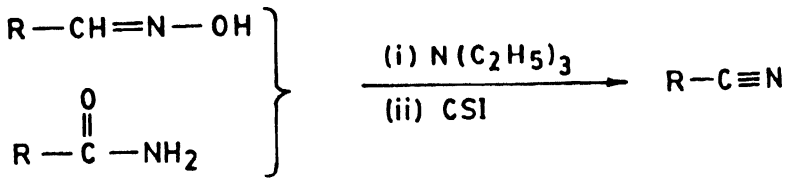
CSI acts as an effective and mild dehydrating agent in the facile conversion of aldoximes and amides into corresponding nitriles.[90] CSI can also be used in derivatization of carboxylic acids,[91] *i.e.*, to the corresponding anhydrides, amides and esters as depicted in Scheme I.4.2.

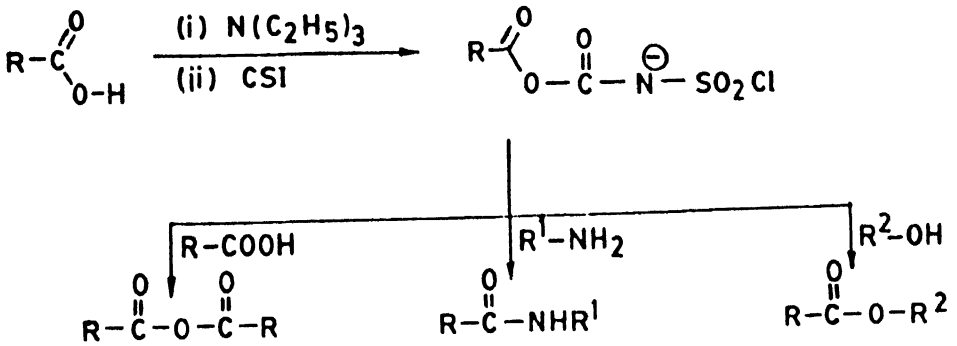
1.4.5 Electrophilic aromatic substitution reactions

The aromatic compounds which readily undergo electrophilic substitution reactions, react with CSI to produce the corresponding

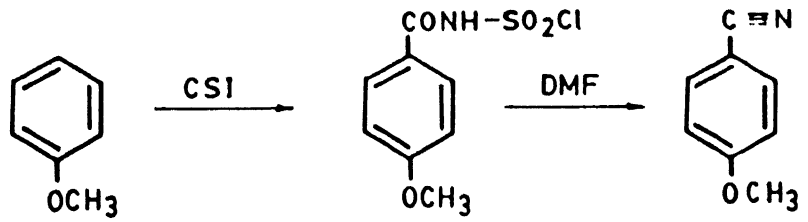
N-chlorosulfonyl carboxamides.[36,92,93] These can be converted to the corresponding nitriles in good yield, by reaction with dimethyl formamide. This reaction provides a mild and efficient one-flask synthesis of aromatic nitriles (Scheme I.4.3).

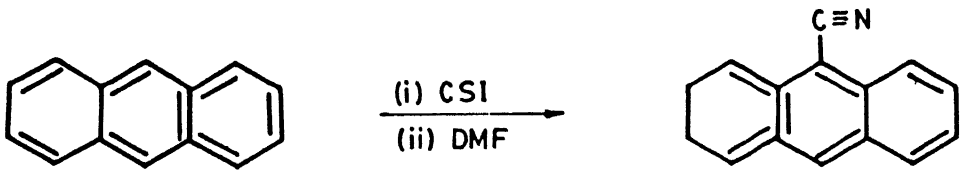
SCHEME 1.4.2

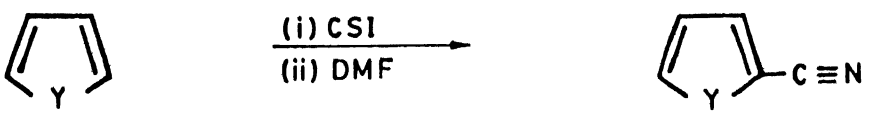




SCHEME 1.4.3



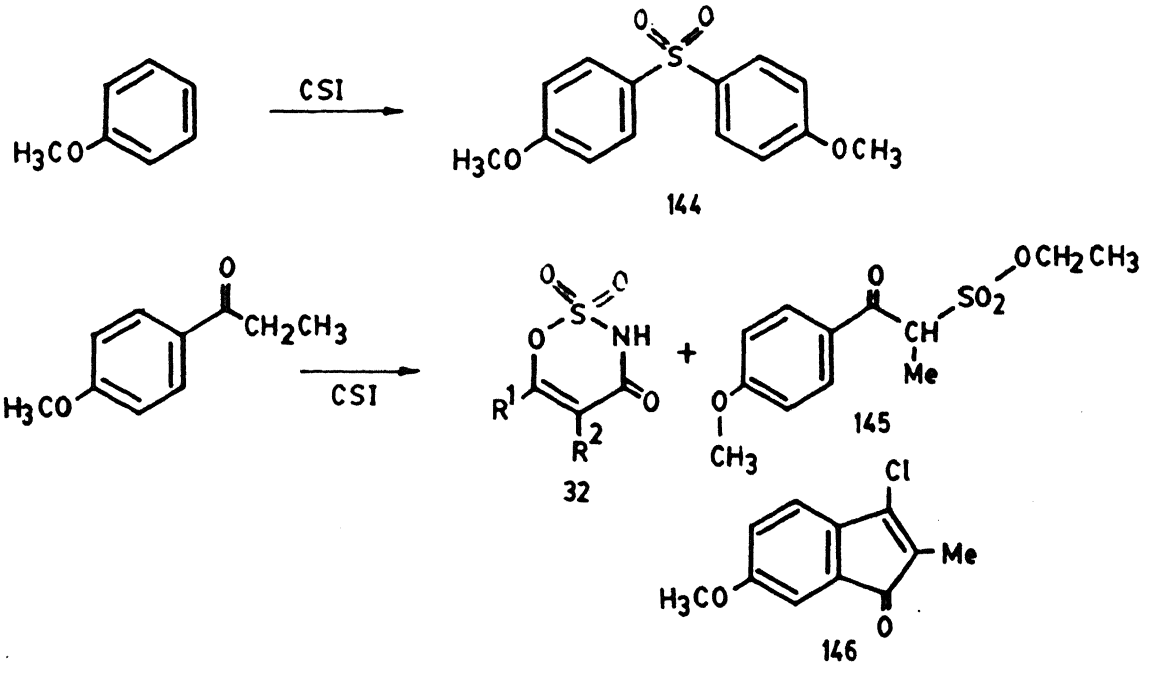




1.4.6 Reaction with phenolic ethers

An interesting reaction occurs between CSI and anisole,[94] the only product isolated being *bis*-(4-methoxyphenyl) sulfone (**144**). CSI reacts with *p*-methoxyacetophenone[32] to give the unusual products *viz.*, oxathiazine dioxide (R_1= *p*-MeO-Ph, R_2= Me; 3%) (32), ethyl-*p*-methoxypropiophenone-α-sulfonate (40%) (145) and 3-chloro-6-methoxy-2-methyl indenone (3%) (146) (Scheme I.4.4).

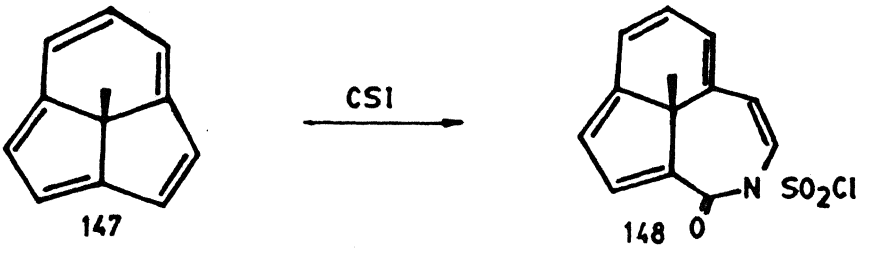
SCHEME I.4.4



1.4.7 Ring expansion reaction

CSI reacts with 7b-methyl-7bH-cyclopent[cd]indene[95] **147** to produce the ring expanded product indenoazepine **148** (Scheme I.4.5).

SCHEME I.4.5



CONCLUSIONS

In conclusion it may be stated that the above cited examples serve to illustrate the versatility of the reagent, chlorosulfonyl isocyanate. It is a highly reactive heterocumulene, and is useful in the synthesis of many heterocycles. This novel reagent finds extensive use not only in the heterocyclic synthesis but also in the preparation of many biologically active compounds which includes antibiotics,[96,97] herbicides, plant growth inhibitors/regulators,[98,99] analgesics, anti-inflammatory,[100,101] neuroleptics,[102] anti-depressants,[103] anti-convulsant,[104] anti-malignant cell growth compounds[105] and penicillin type drugs.[55-59] An overview of literature on the reactions of CSI, indicates that this area of research holds a great promise for further exploration. It is in this context, the work described in the thesis forms a part of our contribution in understanding the chemistry of chlorosulfonyl isocyanate.

REFERENCES

1. R. Graf, *Chem. Ber.*, 1956, **89**, 1071.
2. R, Graf, *Ger. Offen.*, 1955, 928, 896; *Chem. Abstr.*, 1957, **51**, 4419c.
3. R. Graf, *Angew. Chem. Int. Ed. Engl.*, 1968, **7**, 172.
4. J.K. Rasmussen, A. Hassner, *Chem. Rev.*, 1976, **76**, 389.
5. W.A. Szabo, *Aldrichimica Acta*, 1977, **10**, 23.
6. D.N. Dhar, K.S.K. Murthy, *Synthesis*, 1986, 437.
7. A. Kamal, P.B. Sattur, *Heterocycles*, 1987, **26**, 1051.
8. R. Graf., *Chem. Ber.*, 1963, **96**, 56.
9. J.B. Hendrickson, I. Joffee, *J.Am. Chem. Soc.*, 1973, **95**, 4083.
10. H. Hofmann, R. Wagner, J. Uhl, *Chem. Ber.*, 1971, **104**, 2134.
11. G. Lohaus, *Chem. Ber.*, 1972, **105**, 2791.
12. M. Hedayatullah, J.F. Brault, *Phosphorus Sulfur*, 1981, **11**, 303.
13. M.V. García, J.C. Menédez, M. Villacampa, M.M. Söllhuber, *Synthesis*, 1991, 697.
14. A. Kamal, P.B. Sattur, *Synth. Commun.*, 1982, **12**, 157.
15. D.N. Dhar, A.K. Bag, *Ind. J. Chem.*, 1983, **22B**, 627.
16. A. Kamal, P.B. Sattur, *Synthesis*, 1981, 272.
17. D.N. Dhar, A.K. Bag, *Ind. J. Chem.*, 1982, **21B**, 366.
18. A. Kamal, Ph.D. Thesis, Aligarh Muslim University, 1982.
19. S. Karady, J.S. Amato, D. Dortmund, A.A. Patchatt, R.A. Reamer, R.J. Tull, L.M. Weinstock, *Heterocycles*, 1979, **12**, 815.
20. S. Karady, J.S. Amato, D. Dortmund, A.A. Patchatt, R.A. Reamer, R.J. Tull, L.M. Weinstock, *Heterocycles*, 1979, **12**, 1199.

21. Y. Girard, J.G. Atkinson, J. Rokach, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1043.

22. R. Sarges, H.R. Howard, Jr., P.R. Kelbaugh, *J. Org. Chem.*, 1982, **47**, 4081.

23. A. Kamal, K.R. Rao, P.B. Sattur, *Synth. Commun.*, 1980, **10**, 799.

24. J.S. Kang, D.Y. Oh, *Heterocycles*, 1986, **24**, 2255.

25. H.Wamhoff, M. Ertas, *Synthesis*, 1985, **2**, 190.

26. J. Daniel, D.N. Dhar, *Synth. Commun.*, 1993, **23**, 121.

27. E. Otto, W. Duerckheimer, R. Muschaweck, *German Patent*, 2, 409, 355 (1975); *Chem. Abstr.*, 1976, **84**, 59606q.

28. M. Hedayatullah, J.F. Brault, *Phosphorus Sulfur*, 1981, **11**, 255.

29. K. Clauss, H.J. Friedrich, H. Jensen, *Justus Liebigs Ann. Chem.*, 1974, 561.

30. J.K. Rasmussen, A. Hassner, *J. Org. Chem.*, 1973, **38**, 2114.

31. J.K. Rasmussen, A. Hassner, *Synthesis*, 1973, 682.

32. A. Hassner, J.K. Rasmussen, *J. Am. Chem. Soc.*, 1975, **97**, 1451.

33. H. Bestian, *Pure Appl. Chem.*, 1971, **27**, 611.

34. K. Clauss *Justus Liebigs Ann. Chem.*, 1969, **722**, 110.

35. N.S. Isaacs, *Chem. Soc. Rev.*, 1976, **5**, 181.

36. R. Graf., *Justus Liebigs Ann. Chem.*, 1963, **661**, 111.

37. R.B. Woodward, R. Hoffman, *Angew. Chem. Int. Ed. Engl.*, 1969, **8**, 781.

38. E.J. Moriconi, W.C. Meyer, *J. Org. Chem.*, 1971, **36**, 2841.

39. K. Clauss, *Tetrahedron Lett.*, 1974, 1271.

40. T.J. Barton, R.J. Rogido, *Tetrahedron Lett.*, 1972, 3901.

41. D.H. Aue, H. Iwahashi, D.F. Shellhamer, *Tetrahedron Lett.*, 1973, 3719.

42. T. Sasaki, S. Eguchi, Y. Hirako, *Tetrahedron*, 1976, **32**, 437.

43. T. Sasaki, K. Hayakawa, T. Manabe, S. Nishida, *J. Am. Chem. Soc.*, 1981, **103**, 565.

44. (a) J.R. Malpass, M.J. Tweddle, *J. Chem. Soc. Chem. Commun.*, 1972, 1247.

(b) L.A. Paquette, T. Kakihana, J.F. Hansen, J.C. Philips, *J. Am. Chem. Soc.*, 1971, **93**, 152.

45. E.J. Moriconi, P.H. Mazzocchi, *J. Org. Chem.*, 1966, **31**, 1372.

46. J. Mann, H.J. Overton, T. Lewis, *Tetrahedron Lett.*, 1985, 6133.

47. G.T. Furst, M.A. Wachsman, J. Pieroni, J.G. White, E.J. Moriconi, *Tetrahedron*, 1973, **29**, 1675.

48. J.R. Malpass, *Tetrahedron Lett.*, 1972, 4951.

49. T. Sasaki, S. Eguchi, H. Yamada, *J. Org. Chem.*, 1973, **38**, 679.

50. K. Clauss, D. Grimm, G. Prossel, *Justus Liebigs Ann. Chem.*, 1974, 539.

51. P.H. Bentley, G. Brooks, M.L. Gilpin, E. Hunt, *Tetrahedron Lett.*, 1979, 1859.

52. G. Gosteli, H. Pfaender, R.B. Woodward, *J. Am. Chem. Soc.*, 1980, **102**, 2039.

53. P. Lombardi, G. Franceschi, R. Arcamone, *Tetrahedron Lett.*, 1979, 3777.

54. S. Odia, A. Yoshida, *J. Antibiot.*, 1980, **33**, 107.

55. M. Lang, K. Prasad, W. Holick, J. Gosteli, I. Ernes, R.B. Woodward, *J. Am. Chem. Soc.*, 1979, **101**, 6296.

56. K. Hirai, *J. Synth. Org. Chem.*, 1980, **38**, 2.

57. J.D. Buynak, M.N. Rao, H. Pajouhesh, R.K. Chandrasekaran, K. Finn, P. deMeester, S.C. Chu, *J. Org. Chem.*, 1985, **50**, 4245.

58. C.H. Alfred, C.J. Charles, E.L. Godfrey, W.E. McKenzie, *Ger. Offen. D.E.*, 1984, 3, 327, 449; *Chem. Abstr.*, 1984, **101**, 78882n.

59. G.C. William, H.D.W. Thomas, H.T. Trefor, *Eur. Pat. Appln.* Ep., 1986, 168, 177; *Chem. Abstr.*, 1986, **105**, 78755f.

60. J.D. Buynak, M.N. Rao, *J. Org. Chem.*, 1986, **51**, 1571.

61. E.J. Moriconi, W.C. Meyer, *Tetrahedron Lett.*, 1968, 3823.

62. R.J.P. Barends, W.M. Speckamp, H.O. Huisman, *Tetrahedron Lett.*, 1970, 5301.

63. W.E. Volz, L.A. Paquette, R.J. Rogido,T.J. Barton, *Chem. Ind., (London)*, 1974, 771.

64. L.A. Paquette, G.R. Allen Jr., M.J. Broadhurst, *J. Am. Chem. Soc.*, 1971, **93**, 4503.

65. J.C. Jagt, A.M. vanLeusen, *J. Org. Chem.*, 1974, **39**, 564.

66. E.J. Moriconi, Y. Shimakawa, *J. Org. Chem.*, 1972, **37**, 196.

67. E.J. Moriconi, J.F. Kelly, *J. Org. Chem.*, 1968, **33**, 3036.

68. R. Gompper, D. Lach, *Tetrahedron Lett.*, 1973, 2683.

69. M.L. Poutsma, P.A. Ibarbia, *J. Am. Chem. Soc.*, 1971, **93**, 440.

70. E. Mundlos, R. Graf, *Justus Liebigs Ann. Chem.*, 1964, **677**, 108.

71. A.C. Gibbard, C.J. Moody, C.W. Rees, *J. Chem. Soc. Perkin Trans. I*, 1986, 145.

72. P.H. Ferber, G.E. Gream, P.K. Kirkbride, *Tetrahedron Lett.*, 1980, 2447.

73. D.N. Dhar, G. Mehta, S.C. Suri, *Ind. J. Chem.*, 1976, **14B**, 477.

74. S.P. Joseph, K.S.K. Murthy, D.N. Dhar, *Synth. Commun.*, 1989, **19**, 417.

75. J. Daniel, D.N. Dhar, *Tetrahedron*, 1992, **48**, 4551.

76. H. Suschitzky, R.E. Walrond, R. Hull, *J. Chem. Soc. Perkin Trans. I*, 1977, 47.

77. R.E. Walrond, H. Suschitzky, *J. Chem. Soc. Chem. Commun.*, 1973, 570.

79. K.R. Rao, T.N. Srinivasan, P.B. Sattur, *Heterocycles*, 1988, **27**, 683.

80. E.J. Moriconi, C.P. Dutta, *J. Org. Chem.*, 1970, **35**, 2443.

81. (a) D.N. Dhar, R. Raghunathan, *Synthesis*, 1982, 1095.

(b) D.N. Dhar, R. Raghunathan, *Ind. J. Chem.*, 1984, **23B**, 1187.

82. (a) K.S.K. Murthy, D.N. Dhar, *J. Heterocycl. Chem.*, 1984, **21**, 1721.

(b) K.S.K. Murthy, D.N. Dhar, *Synth. Commun.*, 1984, **14**, 687.

83. J. Daniel, D. Shukla, D.N. Dhar, *Chem. Lett.*, 1992, 1975.

84. K.S.K. Murthy, D.N. Dhar, *J. Heterocycl. Chem.*, 1984, **21**, 1699.

85. (a) J. Daniel, D.N. Dhar, *Synth. Commun.*,1993, **23**, 2151.

(b) J. Daniel, D.N. Dhar, *Synth. Commun.*,1991, **21**, 1649.

86. E.S. Kumar, Ph.D. Thesis, I.I.T. Kanpur, 1991, p. 148.

87. D. Gunther, F. Soldan, *Chem. Ber.*, 1970, **103**, 663.

88. K.S.K. Murthy, Y.D. Vankar, D.N. Dhar, *Ind. J. Chem.*, 1983, **22B**, 504.

89. D.N. Dhar, A.K. Bag, *Ind. J. Chem.*, 1983, **22B**, 600.

90. G.A. Olah, Y.D. Vankar, A. Gracia-Luna, *Synthesis*, 1979, 227.

91. K.S.K. Murthy, Y.D. Vankar, D.N. Dhar., *Synthesis*, 1982, 506.

92. G.H. Barnett, H.J. Anderson, C.E. Loader, *Can. J. Chem.*, 1980, **58**, 409.

93. C.E. Loader, H.J. Anderson, *Can. J. Chem.*, 1981, **59**, 2673.

94. F. Effenberger, R. Gleiter, L. Heider, R. Niess, *Chem. Ber.*, 1968, **101**, 502.

95. R. McCague, C.J. Moody, C.W. Rees, *J. Chem. Soc. Perkin Trans.*, *I*, 1984, 175.

96. V.G. barry, *U.S. Patent*, 4, 622, 065; *Chem. Abstr.*, 1987, **106**, 84657n.

97. A. Furlenneier, W. Hofheinz, C.N. Hubschwerlen, H.P. Isenring, *U.S. Patent*, 4, 652, 651; *Chem. Abstr.*, 1987, **107**, 154164w.

98. G. Scheigel, S. Lachhein, H. Berger, *Eur. Pat. Appl.* EP 501, 369 (1992); *Chem. Abstr.*, 1993, **118**, 8613c.

99. V.I. Sorokin, G.V. Kuznetsova, *Can. Pat. Appl.* CA 2, 036,334 (1992); *Chem. Abstr.*, 1993, **118**, 169122g.

100. S.B. Kadin, *Eur. Pat. Appl.*, EP 208, 510; *Chem. Abstr.*, 1987, **106**, 138254z.

101. M.S. Aashwood, B.C. Bishop, P.G. Houghton, G.R. Humphery, *Eur. Pat. Appl.*, EP 500, 171 (1993); *Chem. Abstr.*, 1993, **118**, 6853g.

102. R. Ziegler, P. Neumann, W. Halfliger, *Brit. U.K. Pat. Appl.*, GB. 2, 185, 173; *Chem. Abstr.*, 1987, **107**, 198727m.

103. R. Ziegler, P. Neumann, W. Halfliger, *German Offen,* DE 3, 700, 825; *Chem. Abstr.*, 1987, **107**, 217905n.

104. B.E. Maryanoff, S.O. Nortey, J.F. Gardocki, R.P. Shank, Dodgson, *J. Med. Chem.*, 1987, **30**, 880.

105. T. Nagai, I. Miyokan, I. Kitayama, T. Funaki, N. Tabiie, M. Miyahara, T. Hori, *Japn. Kokai Tokkyo Koho*, JP 663, 101, 63, 101, 391; *Chem. Abstr.*, 1990, **112**, 660w.

CHAPTER-II

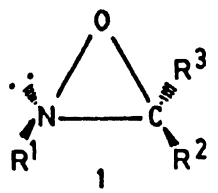
REACTION OF CHLOROSULFONYL ISOCYANATE WITH OXAZIRIDINES

II.1 ABSTRACT

The reaction of chlorosulfonyl isocyanate (CSI) with oxaziridines have been studied in detail. The oxaziridines **33** (**a-n**) upon reaction with CSI at 0-5°C followed by flash column chromatography, furnished 4-chlorosulfonyl-1,2,4-oxadiazolidin-5-one derivatives **34** (**a-n**) in good yields. This cycloadduct can be transformed into corresponding 1,2,4-oxadiazolidin-5-ones **35** (**a-n**), by mild hydrolysis brought about by sodium sulfite and a base. These observations can be rationalized in terms of the following mechanism. Thus, the lone pair of electrons on oxygen atom of the oxaziridine ring attacks the isocyanate group of CSI to give an oxonium ion. The oxonium ion formed being highly unstable results in the cleavage of C-O bond leading to the 1,5-dipolar species **37**, which cyclizes to give 4-chlorosulfonyl-1,2,4-oxadiazolidin-5-one **34**. The cleavage of C-O bond is favoured since it leads to a stable benzylic or tertiary carbocation (*vide infra*, scheme II.3.2). All the products **34** (**a-n**) and **35** (**a-n**) were characterized by their analytical and spectral data. The reaction can serve as a simple method for the conversion of oxaziridines to 1,2,4-oxadiazolidin-5-ones.

II.2 INTRODUCTION

Chlorosulfonyl Isocyanate (CSI) is an extremely versatile reagent and is chemically the most reactive isocyanate known. This reagent finds extensive use in the synthesis of various heterocyclic ring systems. Many reactions of CSI with small ring heterocycles, *viz.*, oxiranes, aziridines, azirines, oxetanes are well reported in literature (*vide* Chapter I), but so far no attention has been paid to explore its reactivity towards a three membered heterocycle containing oxygen and nitrogen atom in ring *viz.*, oxaziridine **1**.



1

Oxaziridines[1,2] **1** in general are highly reactive molecules that display novel and unusual chemistry.[3-7] The high reactivity of oxaziridine is related to the strain in the ring and the relatively weak N-O bond. The basicity of oxaziridine nitrogen is less as compared to amines. Nitrogen atom of oxaziridine possesses a stable configuration at room temperature. This property is supported by the fact that optically active as well diastereomeric oxaziridines with E/Z-configuration[3] were prepared.

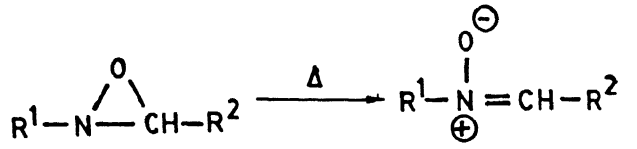
Ring opening of the strained oxaziridine is the key step in all the synthetically useful reactions. Oxaziridines behave as both aminating and oxygenating reagents with nucleophiles. The site of nucleophilic attack at the oxaziridine ring system is determined by the substitution pattern at nitrogen atom.[8] Oxaziridines act exclusively as neutral mild aprotic oxidizing agents with various

nucleophilic systems. Oxaziridines are prepared in optically active[3,9] forms and are highly chemoselective oxidising reagents.[10] Chiral 2-sulfonyloxaziridines react with sulfides to give optically active sulfoxides[11] and have been used in the asymmetric synthesis of many natural products.[12,13] Optically active oxaziridines react with olefins to give chiral epoxides.[14]

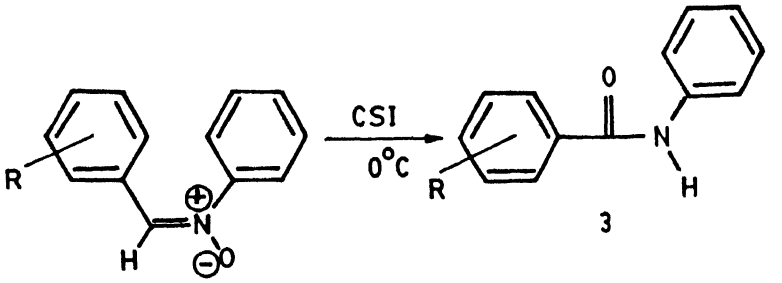
Oxaziridines are the isomers of the nitrones[15] (*vide infra*, Scheme II.2.1). Thermal rearrangement of oxaziridines to nitrones **2** which involves the cleavage of the C-O bond, resulting in the development a positive charge on the ring carbon atom. Joseph and Dhar[16,17] have reported the rearrangement of nitrones to amides **3**, enamides **4** and pyrroles **5** involving the use of CSI. However, there is no report on the formation of a stable (3+2) cycloadduct by the reaction of nitrones with CSI. Nitrones on the other hand undergo 1,3-dipolar cycloaddition with aryl isocyanates[18,19] to yield 1,2,4-oxadiazolidin-5-ones **6**.

Komatsu *et al.*[20] have reported the reaction of oxaziridines with various heterocumulenes *viz.*, ketene, isocyanate and carbodiimide to afford various types of heterocyclic compounds. 2-Alkyl-3-aryloxaziridines undergo cycloaddition with diphenylketene to give oxazolidinone **7**, aldehyde, substituted succinimide **8** and isoquinolinedione **9** derivatives. On the other hand 2-*tert*-butyl-3-phenyloxaziridine on reaction with diphenylketene gave only N-*tert*-butylbenzamide (**10**). The course of reaction depends on the steric hindrance on the nitrogen atom of oxaziridine ring (Scheme II.2.2).

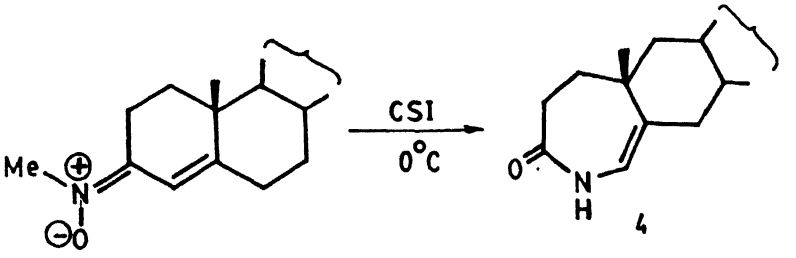
SCHEME II·2·1



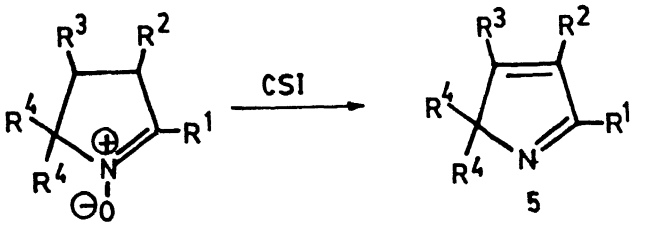
2



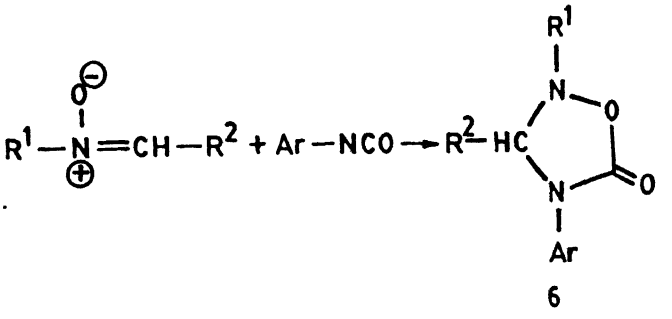
3



4

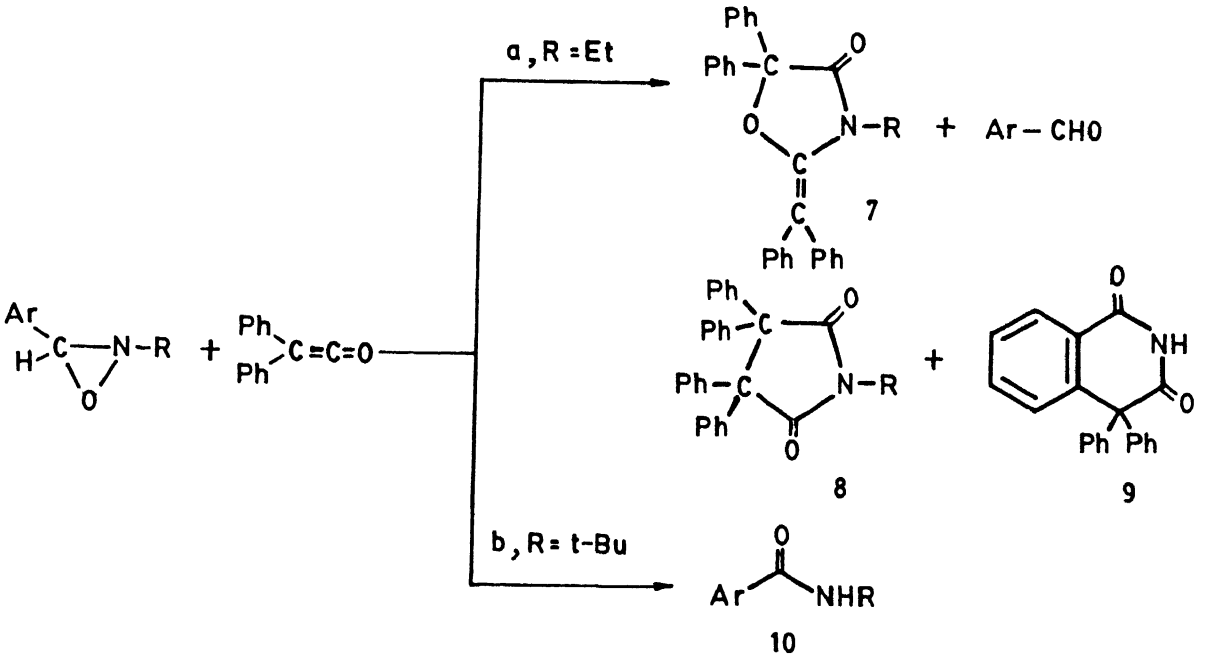


5



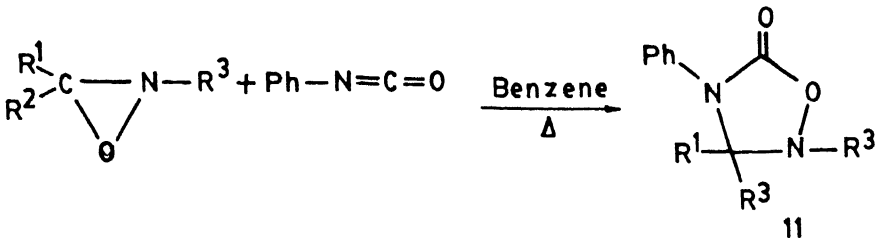
6

SCHEME II·2·2

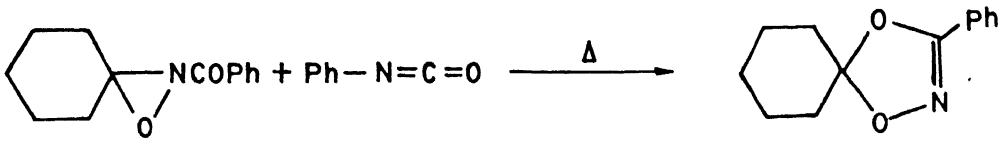


Oxaziridines undergo cycloaddition with phenyl isocyanate[20] at higher temperature to yield oxadiazolidinones 11. The formation of oxadiazolidinone was independent of the N-alkyl substituents. The reaction was initiated by the nucleophilic attack of oxygen atom of oxaziridine on the electrophilic heterocumulene, namely, phenyl isocyanate. N-acyloxaziridine did not form cycloadduct with phenyl isocyanate but gets isomerized to dioxazoline 12 as shown in Scheme II.2.3.

SCHEME II·2·3



11

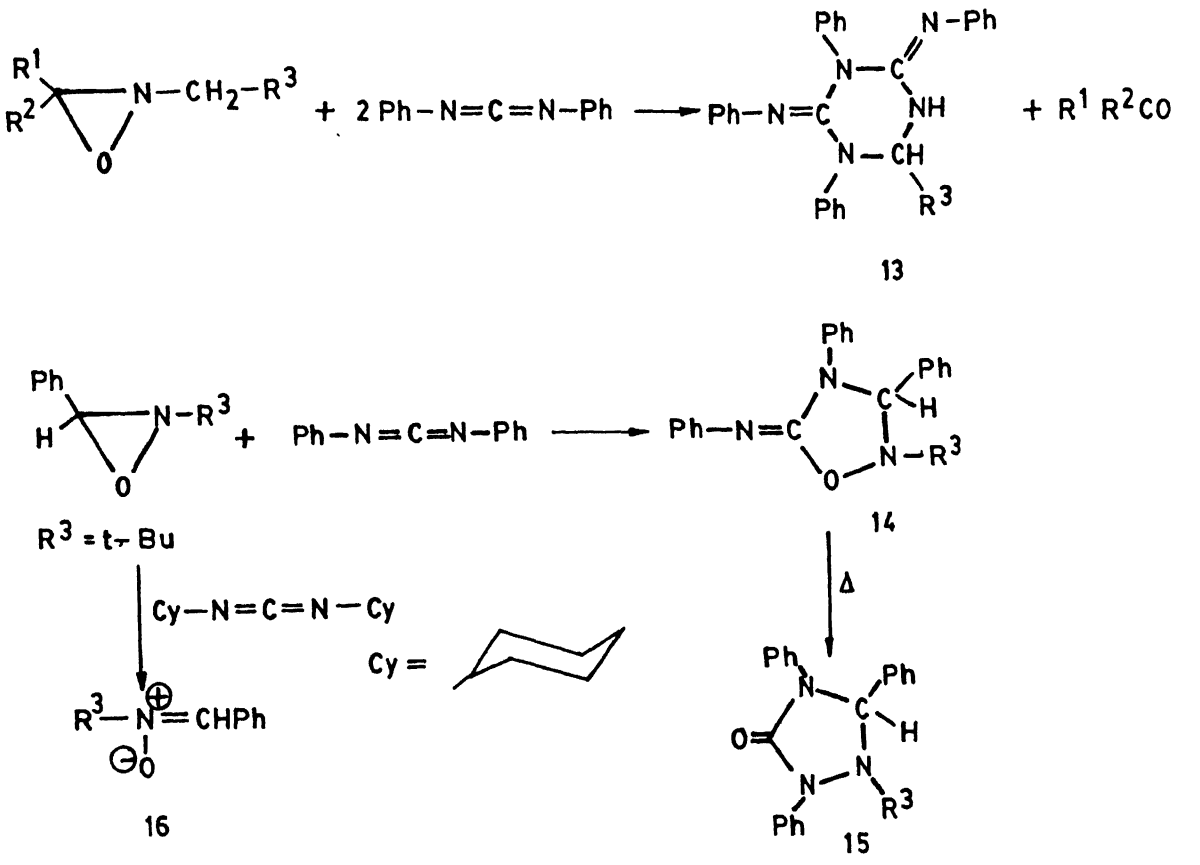


12

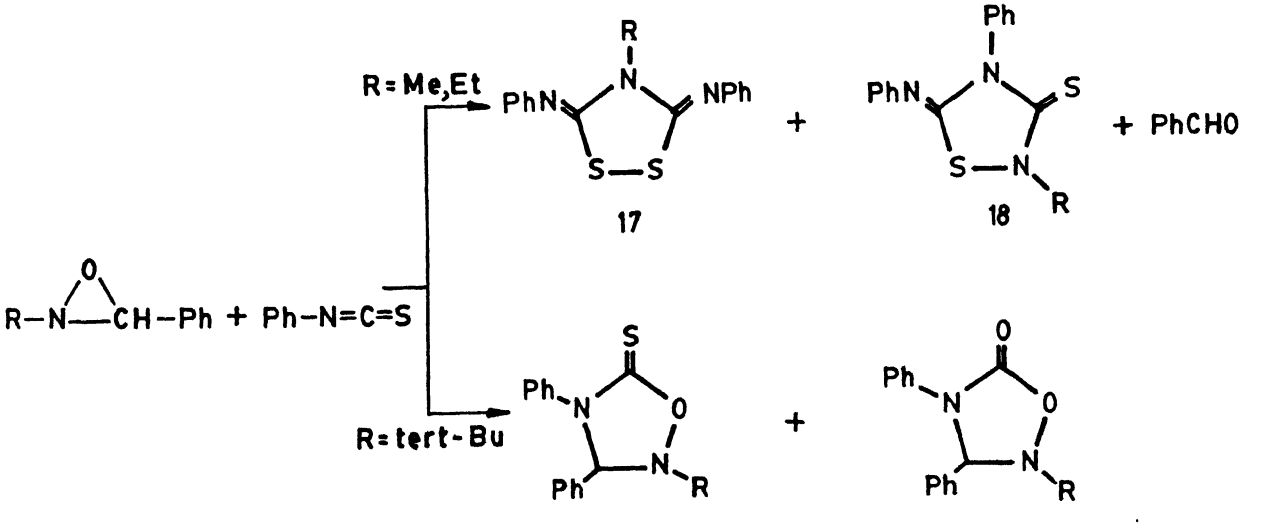
The reaction of N-alkyl oxaziridines with two mole equivalents of diphenyl carbodiimide[20] gave hexahydro-1,3,5-triazine derivative **13** and a ketone. 2-*tert*-Butyloxaziridine when reacted with diphenyl-carbodiimide gave (1:1) cycloadduct **14** which readily rearranges to triazolidinone **15** upon heating. N,N'-Dicyclohexylcarbodiimide did not give adduct with 2-*tert*-butyloxaziridine, however, the latter compound rearranges to α-phenyl-N-*tert*-butylnitrone (**16**) and the carbodiimide was recovered unchanged (Scheme II.2.4).

N-alkyloxaziridines on reaction with isothiocyanate[21,22] afforded dithiazolidine **17** and thiadiazoline **18** derivatives. However, when 2-*tert*-butyloxaziridine was reacted with phenyl isothiocyanate, it gave (1:1) cycloadducts **19** and **20** (Scheme II.2.5).

SCHEME II.2.4

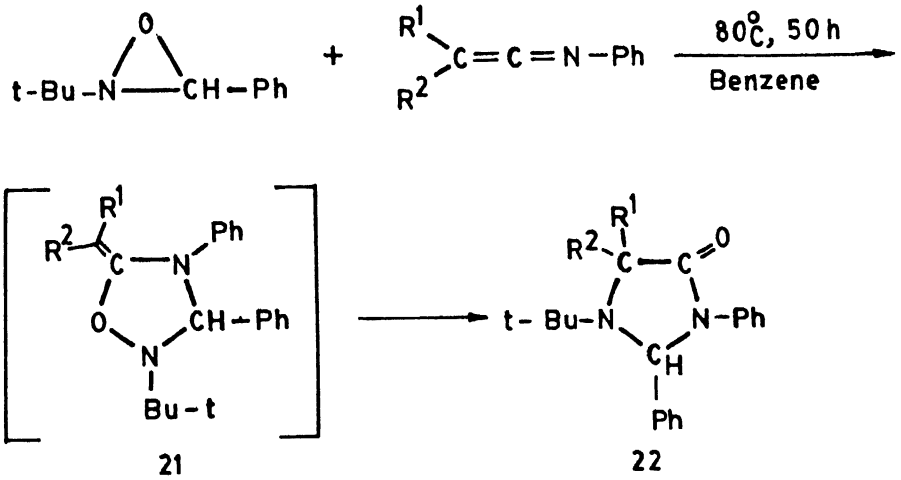


SCHEME II.2.5



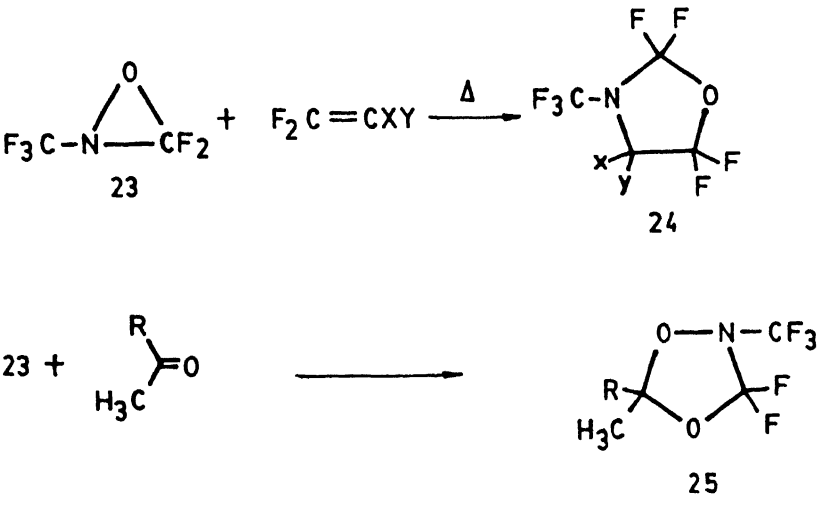
N-arylketeneimines[23] on reaction with oxaziridines produced (1:1) cycloadducts *viz.*, 1,3-diazolidin-4-ones. Thus, dimethylketene-N-phenylimine on reaction with 2-*tert*-butyl-3-phenyloxaziridine gave 1-*tert*-butyl-4,4-dimethyl-2,3-diphenyl-1,3-diazolidin-4-one (22). The reaction mechanism can be explained by cycloaddition across the C=N bond of the cumulative function to form an intermediate cycloadduct 21, which on rearrangement gave 22 (Scheme II.2.6).

SCHEME II·2·6



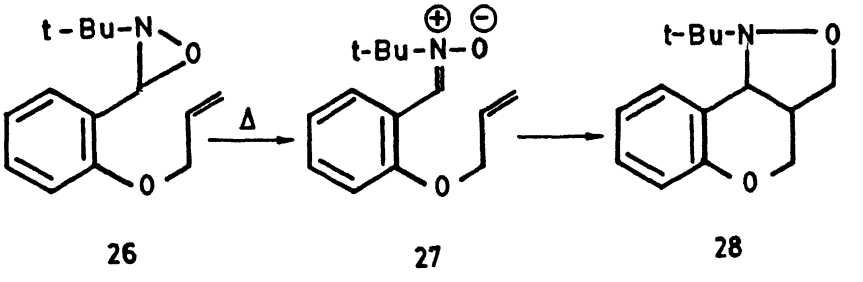
Perfluorooxaziridine (23) reacts regiospecifically with a number of simple 1,1-difluoroolefins[24] under mild conditions to afford good yields of the corresponding 3-(trifluoromethyl) perfluoro-1,3-oxazolidine (24) as shown in Scheme II.2.7. On the other hand, simple olefins produce corresponding oxiranes on reaction with oxaziridine. Perfluorooxaziridine (23) adds readily to ketones[24] to yield 1,3,4-dioxazolidine 25.

SCHEME II.2.7



Padwa and Koehler[25] have reported the intramolecular 1,3-dipolar cycloaddition of oxaziridine 26 to olefin *via* a nitrone intermediate 27 to produce isoxazolidine 28 in good yield as depicted in Scheme II.2.8.

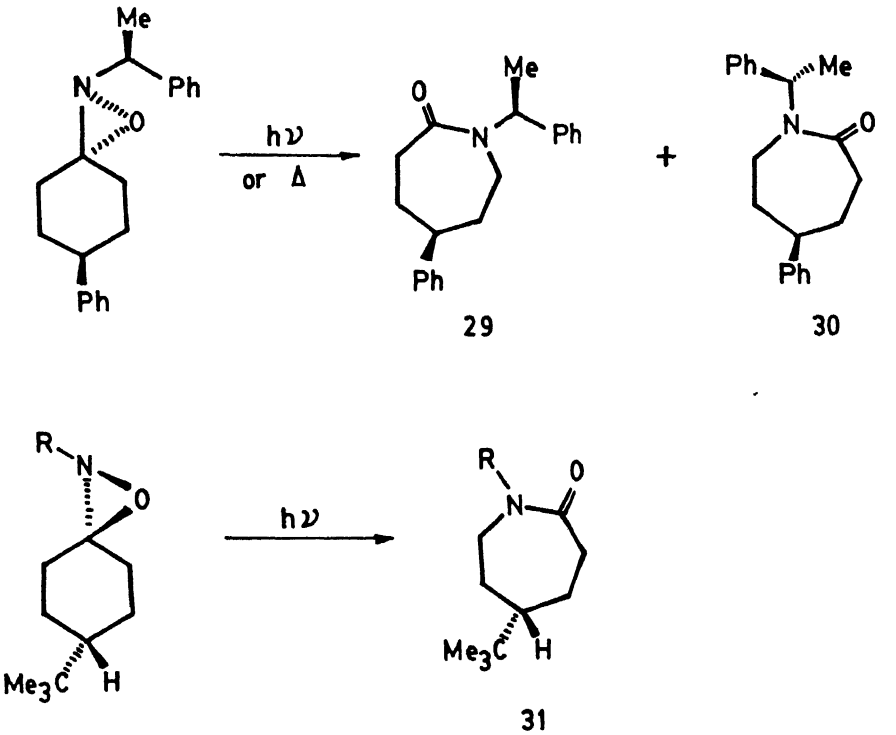
SCHEME II.2.8



Oxaziridines undergo thermal or photochemical isomerisation to amides[26] 29-31. This takes place by the cleavage of the N-O bond and

migration of one of the substituents from carbon to nitrogen atom. Lattes *et al.* showed that the group that migrates is the one which is anti to the nitrogen lone pair.[27] Some of the isomerisation reactions of oxaziridines to lactams[28,29] are shown in Scheme II.2.9.

SCHEME II.2.9



Oxaziridines are also members of the general class of oxidizing reagents.[30] They oxidise various nucleophilic substrate *viz.*, sulfides, selenides olefins, amines, alcohols and ketones by transforming their oxygen atoms as part of a three membered ring. The driving force for the oxygen-transfer by these reagents has been related to relief of ring strain and the formation of strong double bond in the products. N-sulfonyloxaziridines 32 oxidise selectively sulfides[31] to sulfoxides without over oxidation to sulfones.

N-sulfonyloxaziridines epoxidise alkenes in a *syn*-stereospecific manner, *i.e. trans*-alkenes give *trans*-epoxides, while *cis*-alkenes give *cis*-epoxides. Enantiomerically pure oxaziridines enable the asymmetric oxidation of alkenes to produce chiral epoxides.[32,33]

Oxaziridines are important three membered heterocycles. The various reactions with heterocumulenes[20-22] *viz.*, phenyl isocyanate, phenyl isothiocyanate, carbodiimide, ketene, and ketenimine are reported (*vide supra*). They also act as mild aprotic chiral oxidising agents.

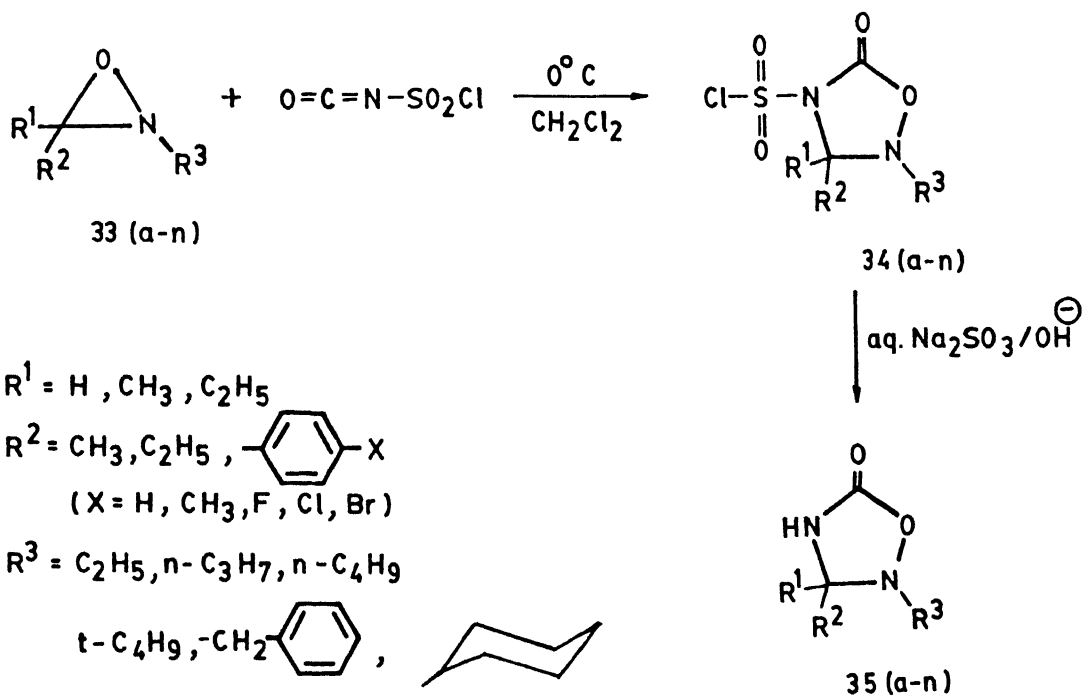
As already discussed nitrones are isomers of oxaziridines. These nitrones undergo rearrangement to corresponding amides[16,17] by the use of chlorosulfonyl isocyanate (Scheme II.2.1). However, oxaziridine with phenyl isocyanate produces a (3+2) cycloadduct. It was, therefore thought worthwhile to study the reaction of CSI with various oxaziridines. The basic aim of this study was to find out whether the reaction gives a rearranged product or a (3+2) cycloadduct.

II.3 RESULTS AND DISCUSSION

In contrast to the other heterocumulene *viz.*, carbodiimide, phenyl isocyanate, ketenes: CSI reacts readily with oxaziridines 33 (**a-n**) in a facile manner. In other words reaction proceeds well under very mild experimental conditions, requiring lower temperature, shorter reaction time and furnishes only one product. Oxaziridines 33 (**a-n**) were synthesised according to the literature procedure, by the reaction of corresponding Schiff's bases (imines) with *m*-chloroperbenzoic acid. All the oxaziridines were isolated in good yields and are collected in Table II.1 (*vide infra*).

The reaction of 2-ethyl-3-phenyloxaziridine (33a) with CSI at low temperature ($0^{o}C$) led to the formation of the [3+2] cycloadduct **34a** in 87% yield. The general reaction of oxaziridine with CSI is shown in Scheme II.3.1.

SCHEME II.3.1



The structure of the heterocycle **34a** was arrived at on the basis of its analytical and spectral data and its chemical transformation into **35a**. The elemental analysis of the compound **34a** with molecular formula $C_{10}H_{11}ClN_2O_4S$, indicated that the compound is a (1:1) adduct of **33a** and CSI. The IR spectrum (Fig. II.1) of **34a** exhibited strong absorption bands at 1780 (ν C=O), 1415 (ν SO_2

and N-SO_2-Cl functions. The ^{1}H-NMR spectrum of **34a** shown in Fig. II.2 contains four resonances, *viz.*, at δ 1.31 (3H, J=7.0 Hz) for methyl protons, a quartet at 3.69 (2H, J=7.0 Hz) for methylene protons, a sharp singlet at 6.33 (1H) due to benzylic proton and a singlet at 7.52 (5H) for aromatic protons. The carbonyl and benzylic carbon atoms of **34a** appeared at δ 151.80 and 91.32 respectively in its ^{13}C-NMR spectrum as shown in Fig. II.3. These ^{13}C-NMR signals are in good agreement with the assigned structure. The structure of adduct **34a** was further supported by its mass spectral fragmentation pattern (Fig. II.4); m/z 290 (M^+), 191 (M^+ - SO_2Cl), 149 (M^+ - CSI), 131 (Ph-C=N-C≡O$^+$), 104 (Ph-CH=N$^{+\cdot}$). Based on the analytical and spectral data it is evident that compound **34a** is formed by the nucleophilic attack by lone pair of the oxygen atom of oxaziridine on to the isocyanate function of CSI. This is followed by cleavage of C-O bond of **36a** and resulted in the formation of stable benzylic carbocation **37a**. This carbocation cyclizes with the nitrogen atom of cumulative function to furnish the 4-chlorosulfonyl-2-ethyl-3-phenyl--1,2,4-oxadiazolidin-5-one (**34a**). This structural assignment was further confirmed by the mild hydrolysis (aqueous sodium sulfite-potassium hydroxide) of the adduct **34a** to the corresponding 2-ethyl-3-phenyl-1,2,4-oxadiazolidin-5-one (**35a**).

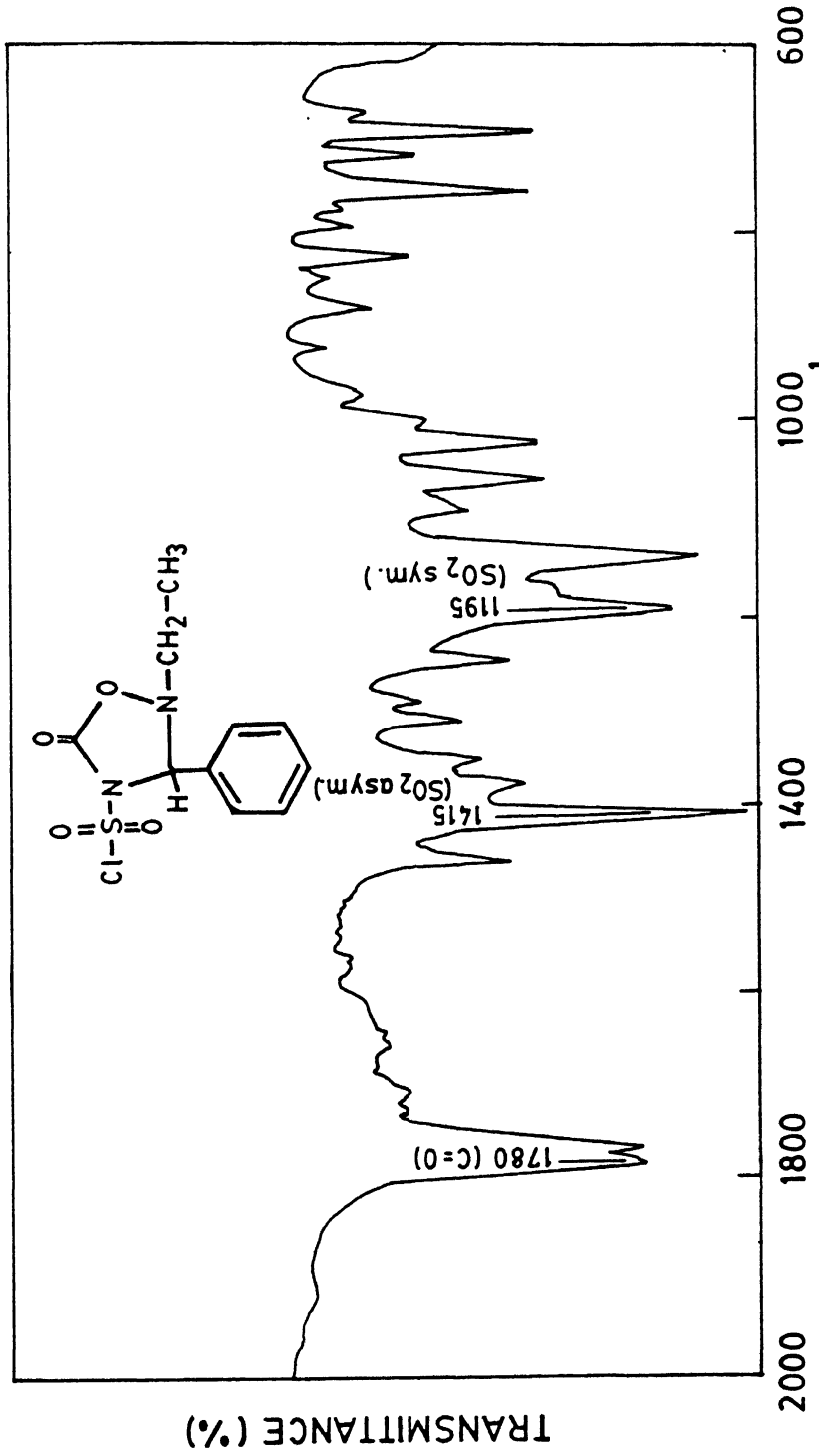


Fig. II.1 IR SPECTRUM OF 34a

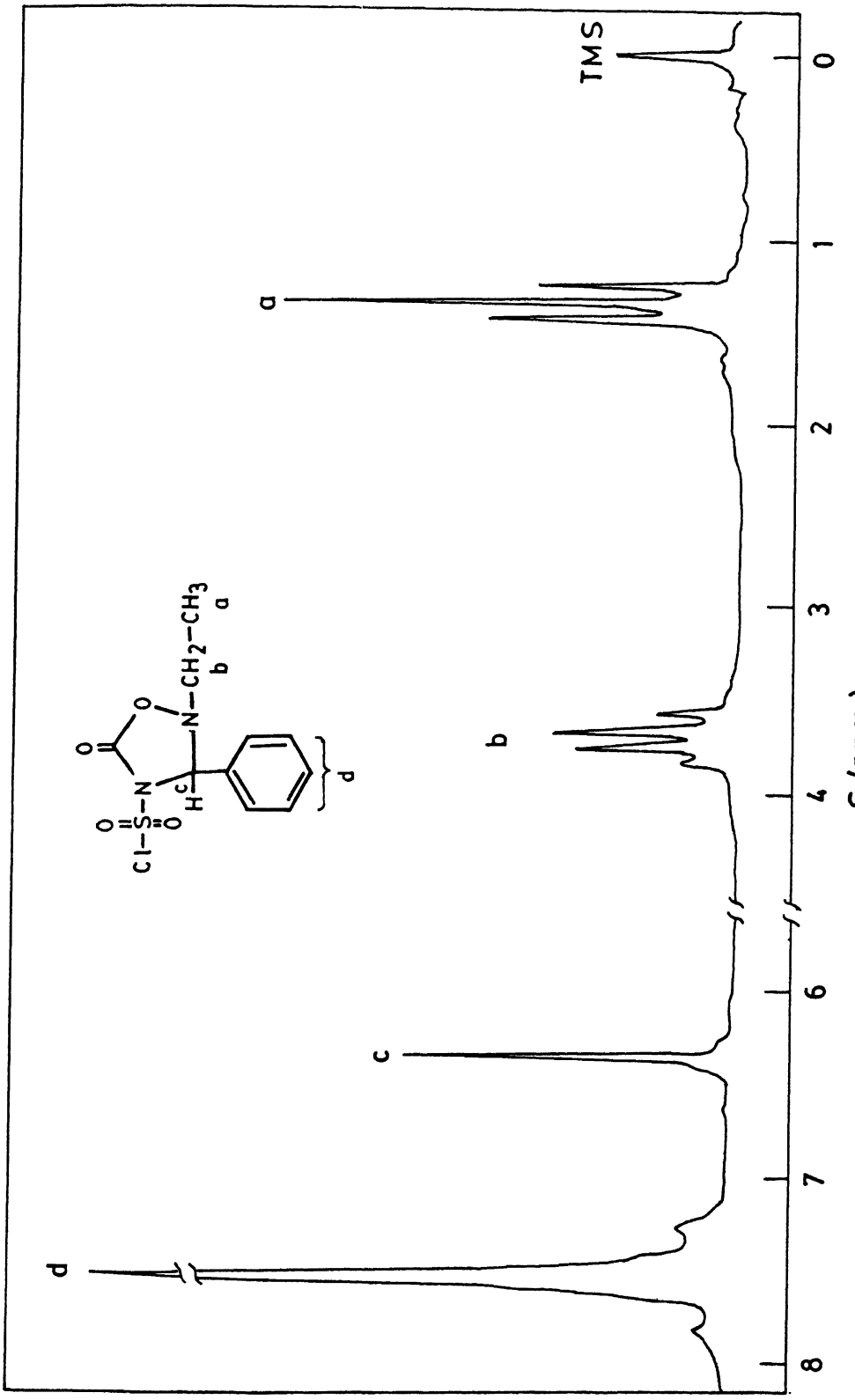


Fig. II.2 ^{1}H-NMR SPECTRUM OF 34a

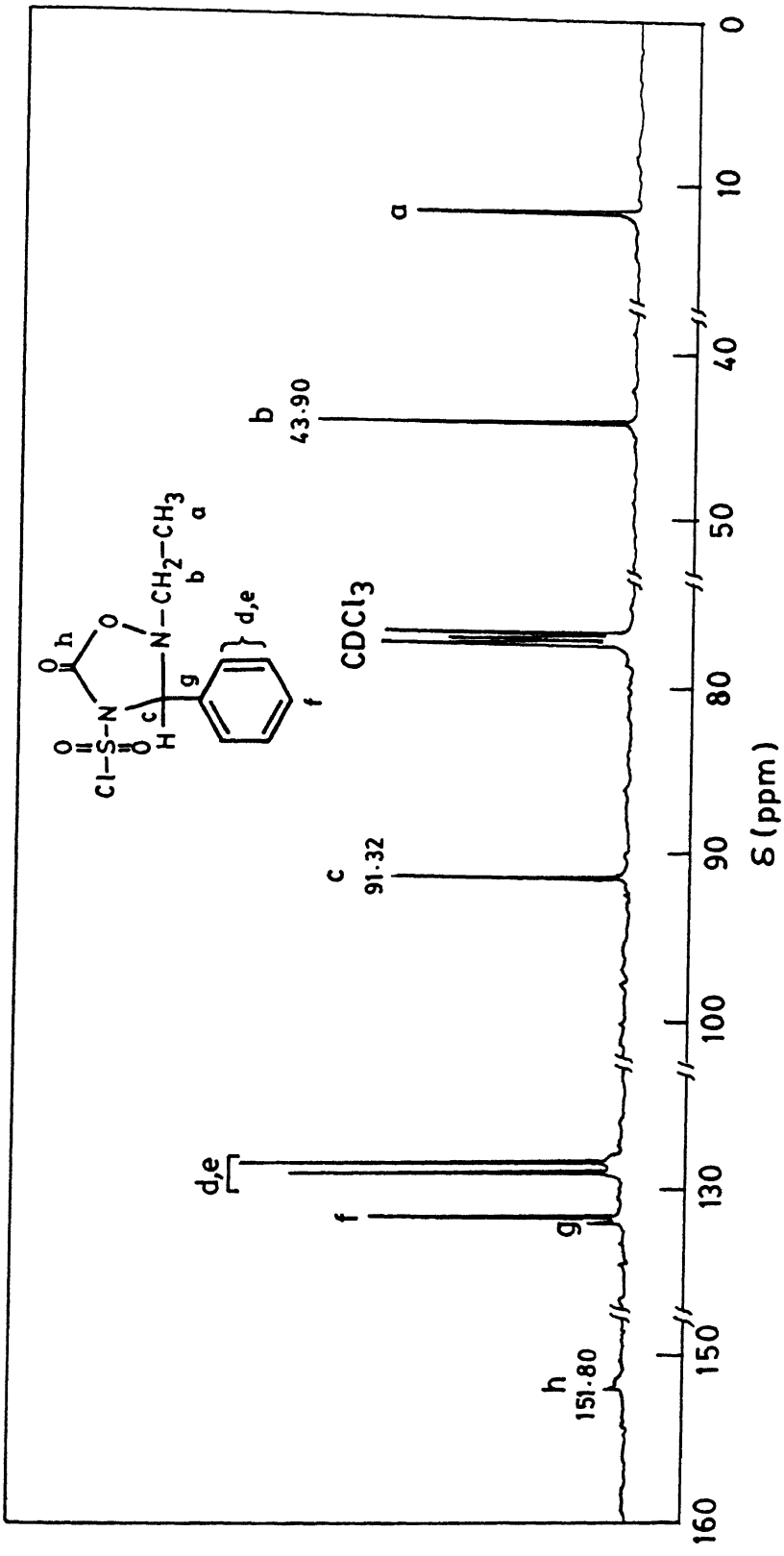


Fig. II·3 ^{13}C-NMR SPECTRUM OF 34a

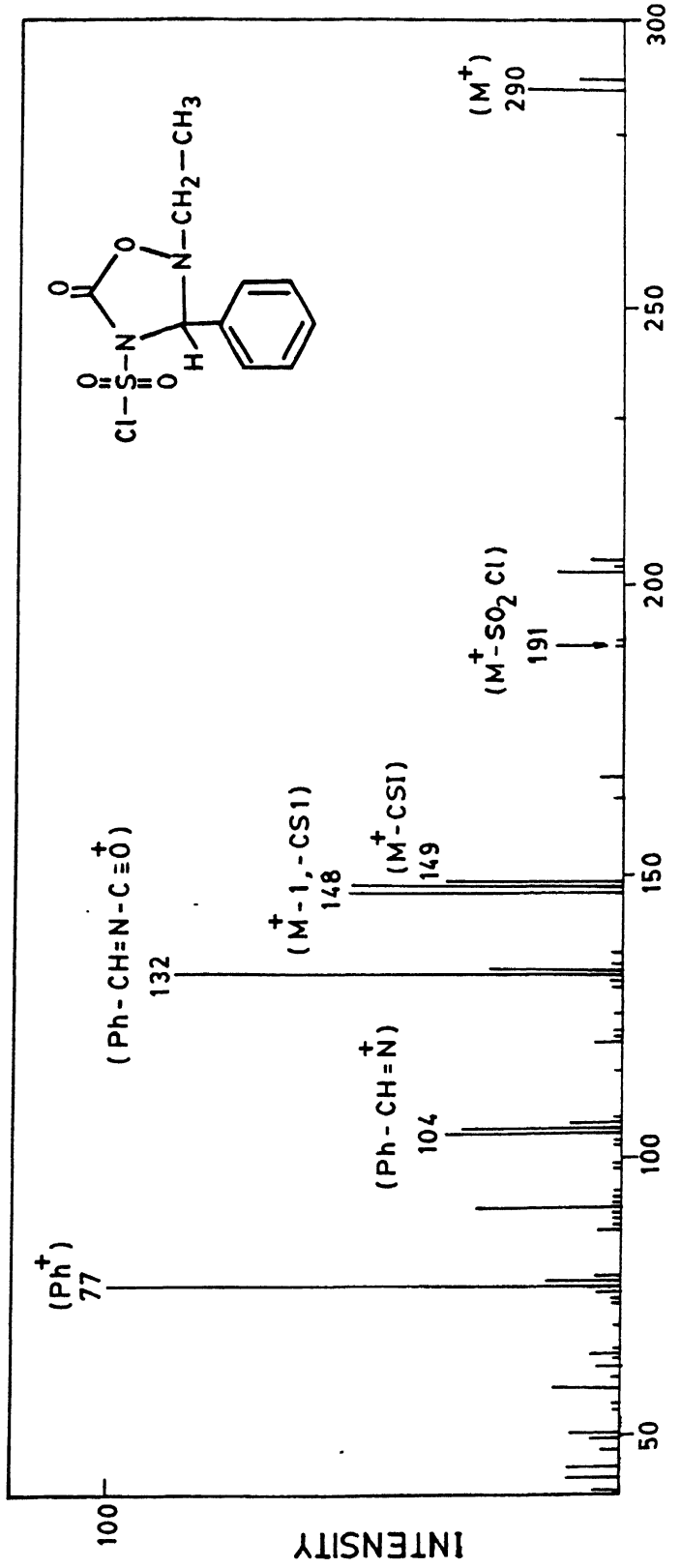


Fig. II. 4 MASS SPECTRUM OF 34a

The structure of hydrolysed product 35a was confirmed by its analytical and spectral data. The analytical data of 35a are in good agreement with the molecular formula: $C_{10}H_{12}N_2O_2$. The IR spectrum of (Fig. II.5) exhibits two characteristic absorption bands at 3225 and 1730 cm^{-1} and are assigned to amide (NH) and carbonyl (NH-CO-O) functions respectively. Absence of sulfonyl absorption bands at 1415 and 1195 cm^{-1} indicated that the chlorosulfonyl group is removed during the hydrolysis. The ^{1}H-NMR spectrum of 35a (Fig. II.6) shows a broad singlet at δ 6.75 (NH), a singlet at 6.09 (1H) for benzylic proton and other signals due to ethyl and phenyl group. The methylene group attached to the nitrogen atom appeared as a multiplet. The ^{13}C-NMR spectrum of 35a (Fig. II.7) shows a down field resonance at δ 163.57 for amide carbon atom (C-5) and the up field signal due to benzylic carbon (C-3) at δ 86.60.

The final proof for the proposed structure of 35a has come from mass spectral data, m/z: 192 (M^+) and other fragment peaks at 149 (M^+ - CONH), 132 (Ph-CH=N-C≡O$^+$), 105 (Ph-CH=NH)$^+$, 104 (Ph-CH≡N)$^+$ as shown in Fig. II.8. Based on the above analytical and spectral data, compound 35a was assigned the structure: 2-ethyl-3-phenyl-1,2,4-oxadiazolidin-5-one.

Aliphatic oxaziridines 33 (a-n) were also prepared. 2-Benzyl-3,3-dimethyloxaziridine (331) was reacted with CSI in an analogous manner to give the corresponding N-chlorosulfonyl cycloadduct 341 as a colorless oil in an overall yield of 57%.. The compound 341 was identified as follows: It shows important IR absorption bands at 1760 (C=O), 1410 (SO_2 asym.) and 1170 cm^{-1} (SO_2 sym.) and indicates the presence of O=C-N-SO_2Cl moiety (Fig. II.9).

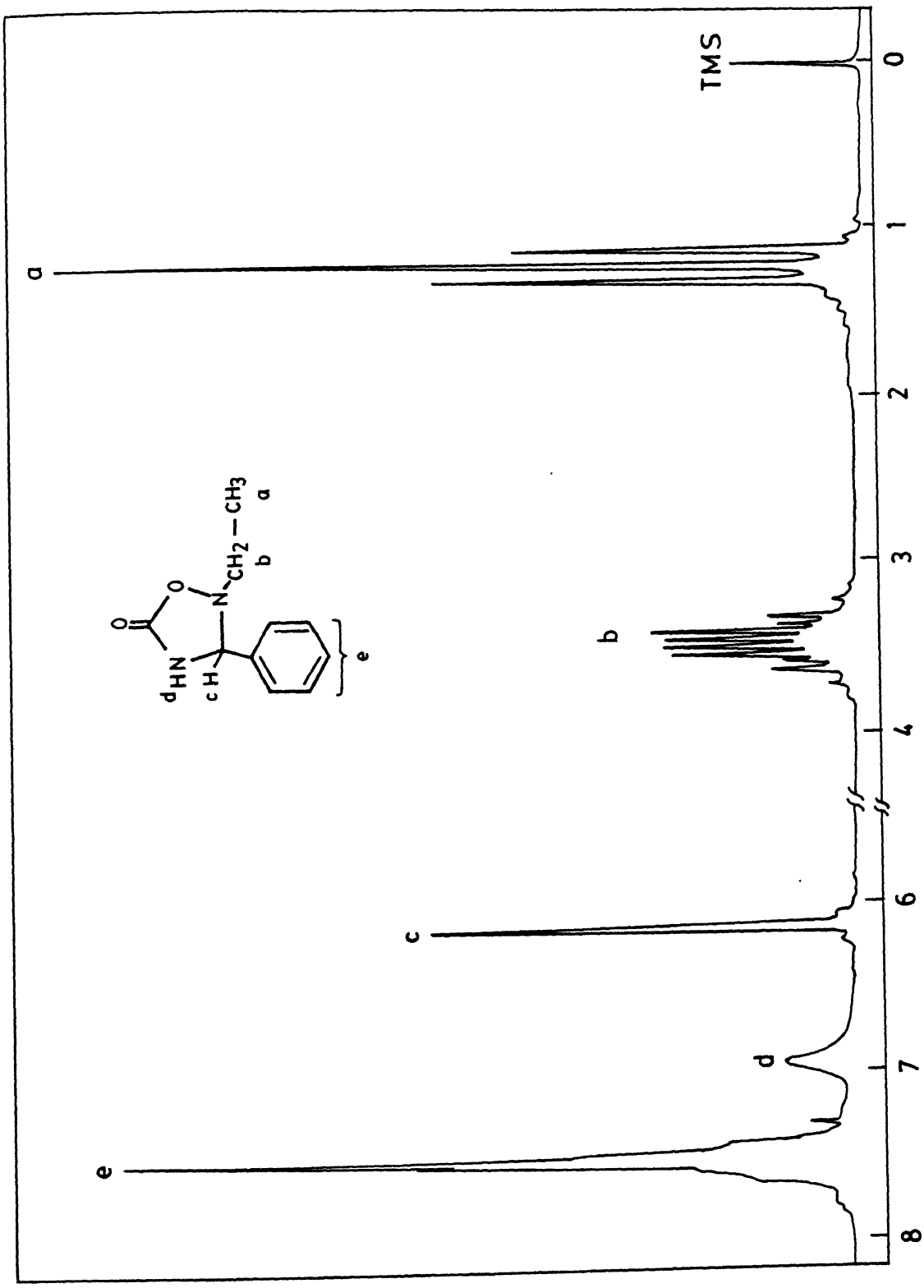


Fig. II.6 ^{1}H-NMR SPECTRUM OF 35a

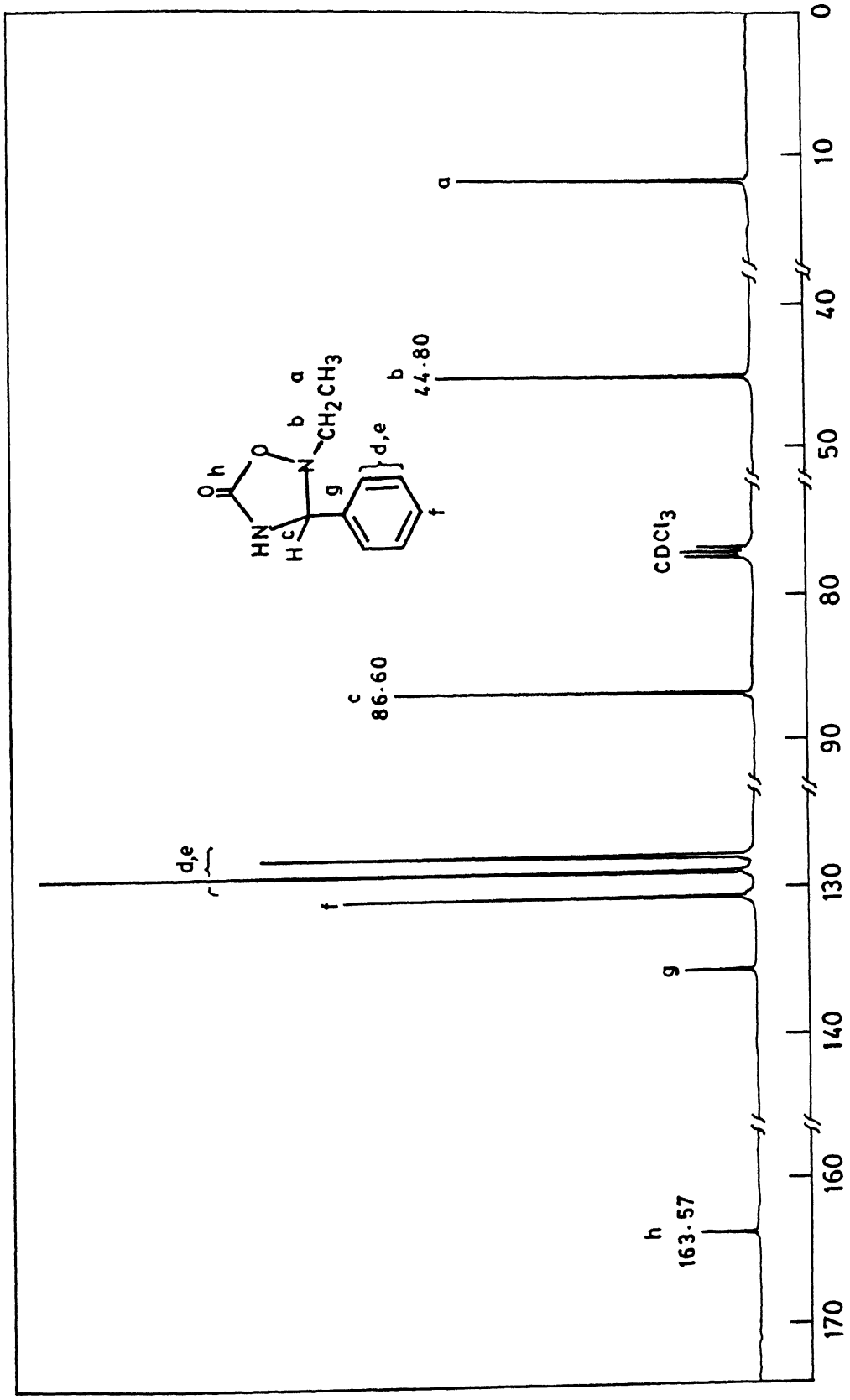


Fig. II.7 ^{13}C-NMR SPECTRUM OF 35a

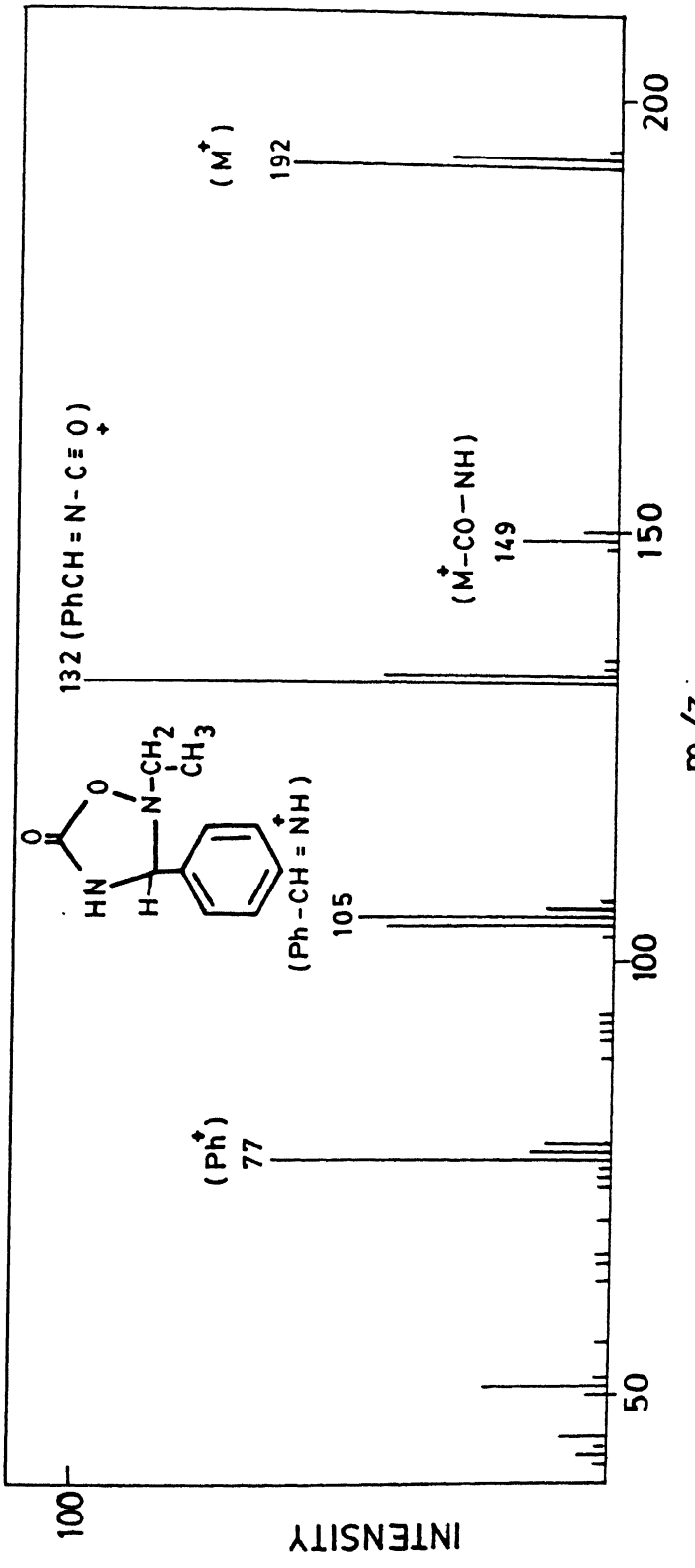


Fig. II.8 MASS SPECTRUM OF 35a

The ^{1}H-NMR (Fig. II.10) shows two singlets at δ 1.42 and 4.42 for methyl and methylene protons and a peak centered at 7.25 for aromatic protons. In the ^{13}C-NMR spectrum (Fig. II.11) of **341** ring carbons C-3 and C-5 appeared at δ 99.38 and 151.74 respectively. The other important signal due to benzylic methylene carbon appeared at δ 51.85.

The structure assignment for **341** was further substantiated by its mass fragmentation pattern: m/z 306 (M^++2), 304 (M^+), 269 (M^+ - Cl), 206 [(M^+ - H) - SO_2Cl], 105 ($Ph-CH_2-N$)$^+$, 91 ($Ph-CH_2$)$^+$, 84 $((CH_3)_2C-N=C\equiv O)^+$ as shown in Fig. II.12.

Analytical data are consistent with the molecular formula $C_{11}H_{13}ClN_2O_4S$. Based on the spectral and analytical data compound **341** was assigned the structure, namely, 2-benzyl-4-chlorosulfonyl--3,3-dimethyl-1,2,4-oxadiazolidin-5-one.

Hydrolysis of compound **341** produced 2-benzyl-3,3-dimethyl-1,2,4-oxadiazolidin-5-one (351) as colorless crystals (65%). The structure of compound **351** was arrived at on the basis of analytical and spectral data. Compound **351** exhibits IR absorption bands at 3255 (NH) and 1730 cm^{-1} (NH-CO-O) (Fig. II.13). The ^{1}H-NMR spectrum shows a broad peak at δ 6.64 (NH exchangeable with D_2O) and other signals due to methyl, methylene and aromatic protons at δ 1.48, 4.52 and 7.33 respectively as shown in Fig. II.14. In the ^{13}C-NMR spectrum shown in Fig. II.15, the ring carbons appear at δ 92.72 (C-3) and 162.43 (C-5).

Final support from mass spectral data (Fig. II.16), m/z: 206 (M^+), 189 (M^+ - CH_3), 163 (M^+ - CONH), 91 ($PhCH_2^+$), 84 ($(CH_3)_2C=N=C=O^+$) and analytical data confirm the structure of

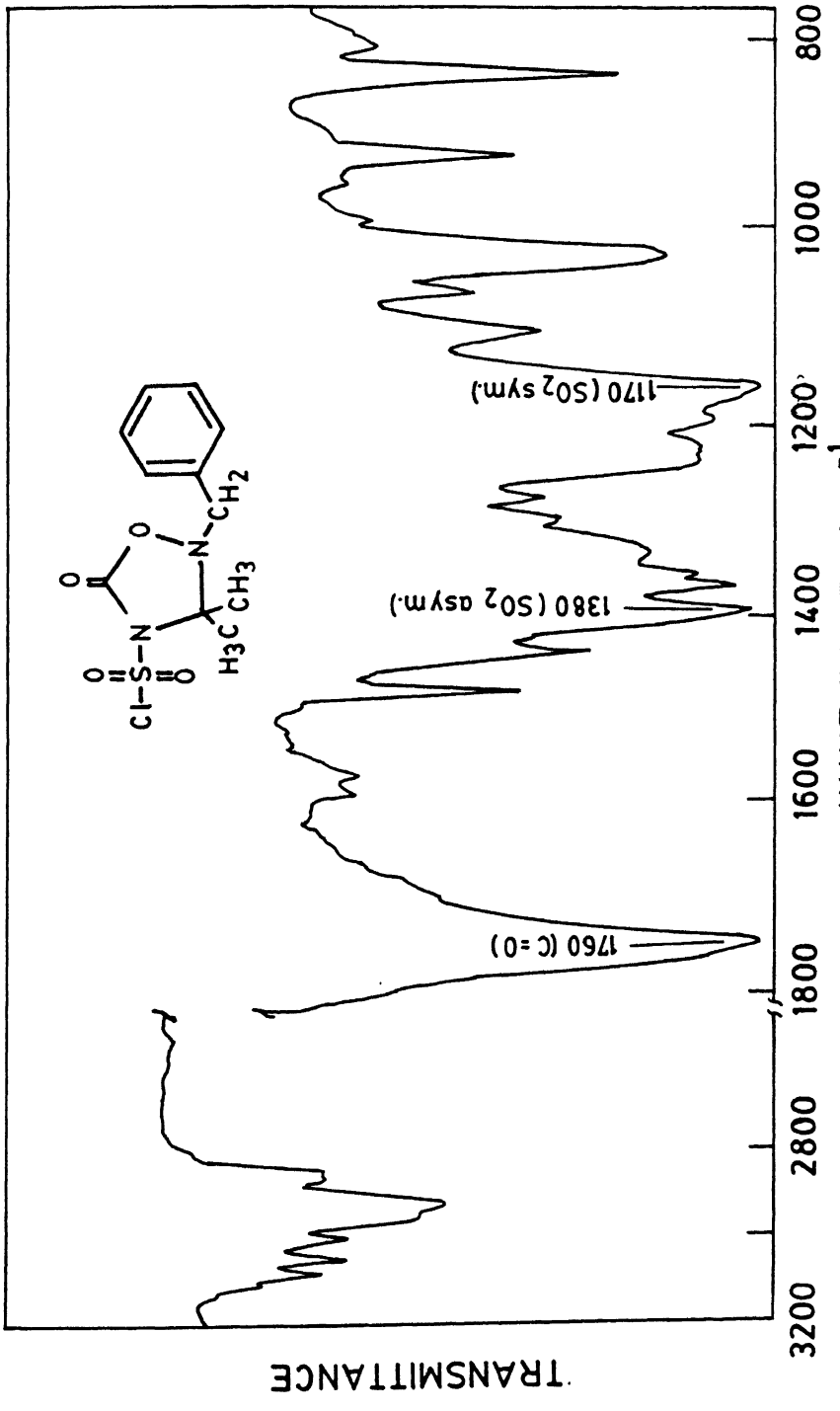


Fig. II.9 IR SPECTRUM OF 341

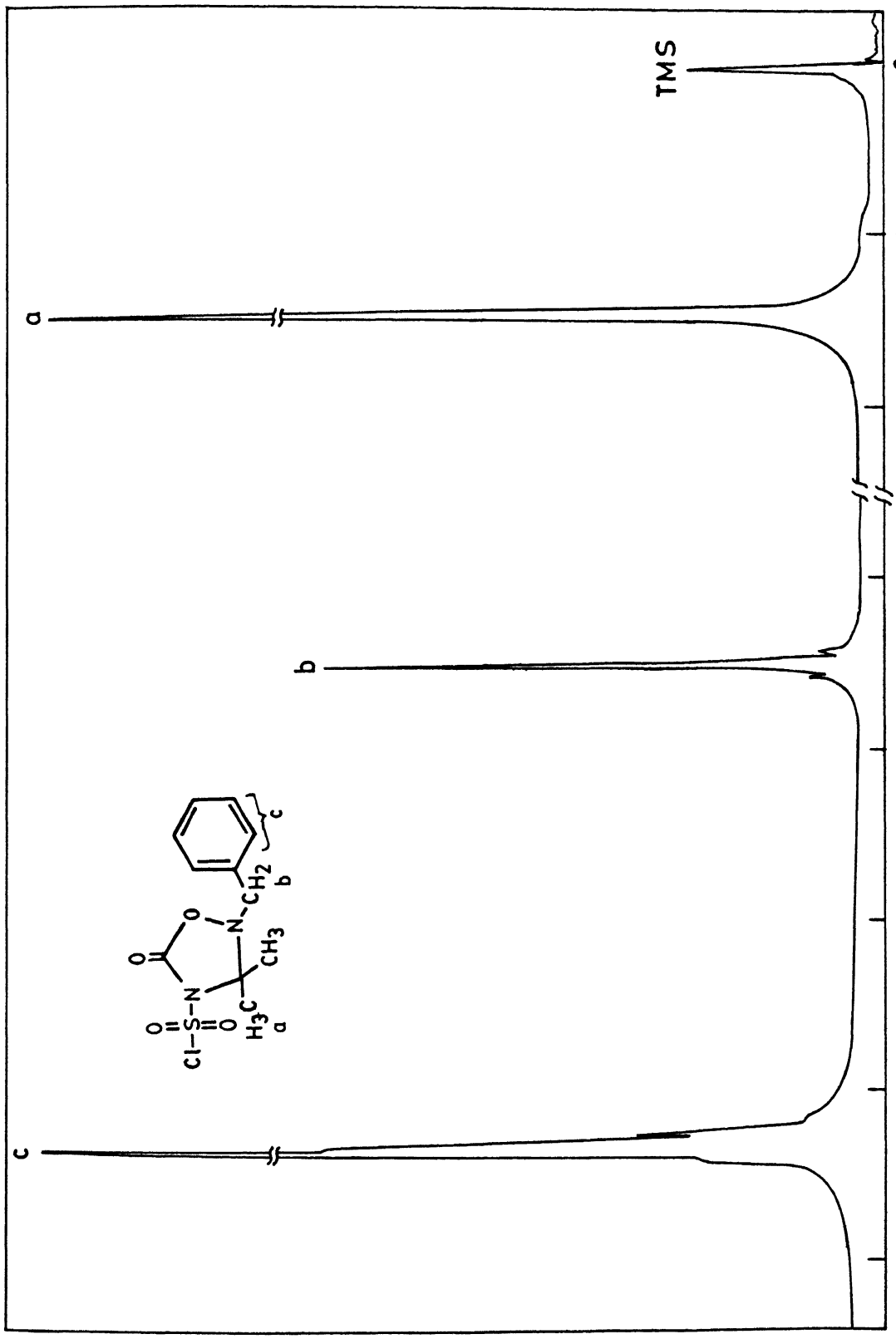


Fig. II·10 ^{1}H-NMR SPECTRUM OF 34I

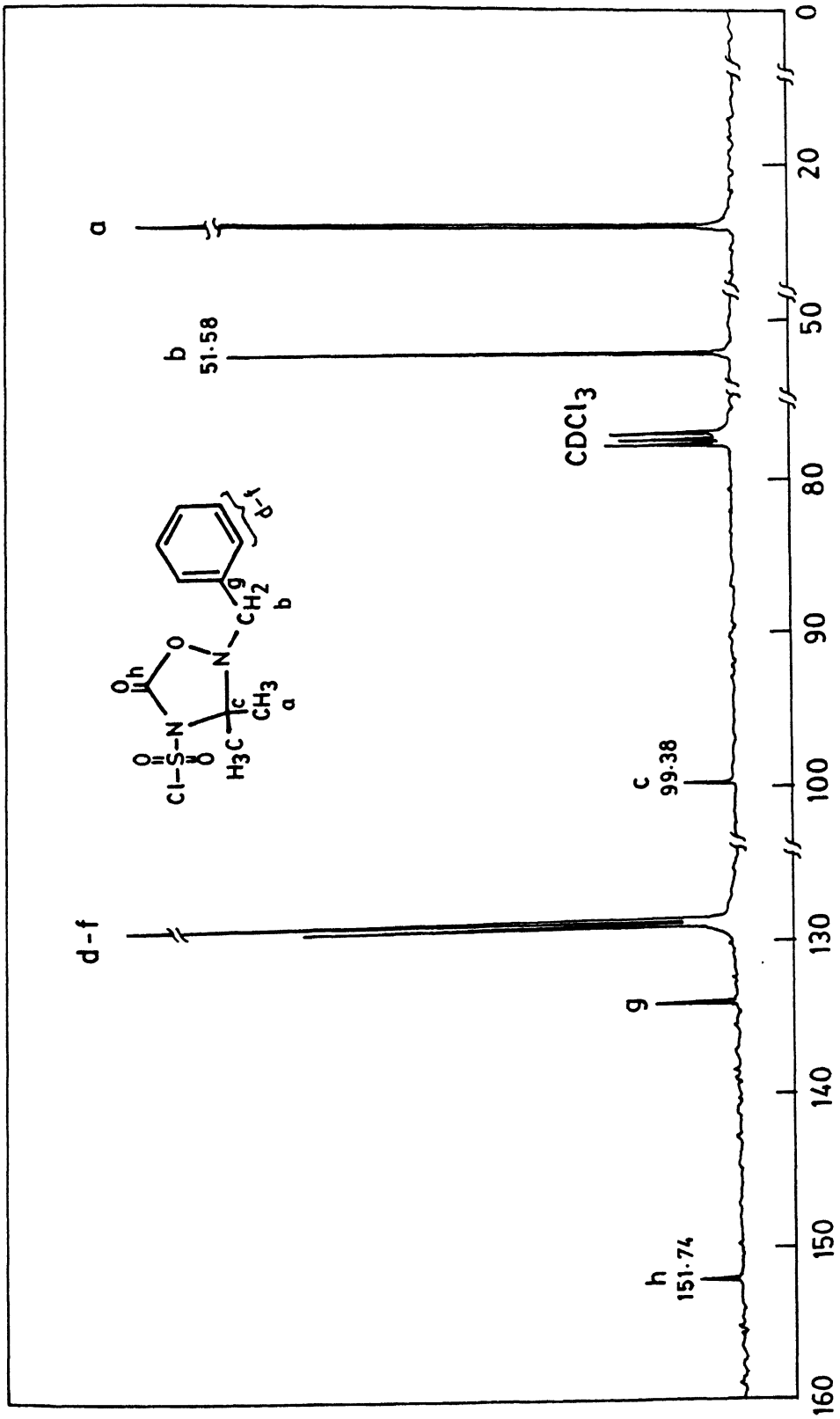


Fig. II.11 ^{13}C-NMR SPECTRUM OF 341

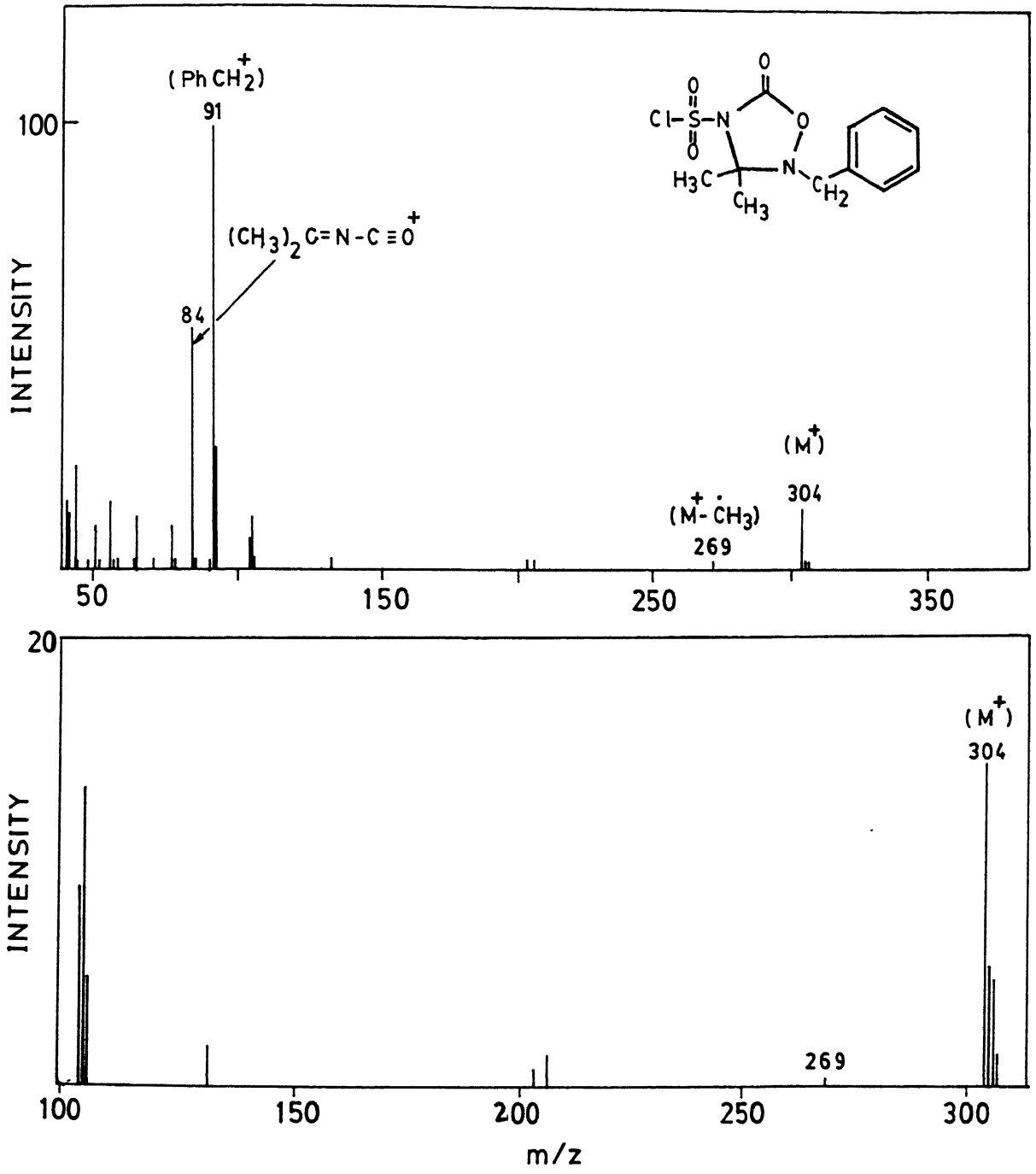


Fig. II-12 MASS SPECTRUM OF 341

compound 35l as 2-benzyl-3,3-dimethyl-1,2,4-oxadiazolidin-5-one.

The ^{1}H-NMR and ^{13}C-NMR data for 1,2,4-oxadiazolidin-5-ones **34** and **35** were compared with known systems, namely, 2-alkyl-3,4-diaryl-1,2,4-oxadiazolidin-5-ones[19] (6) and are found in good agreement with the observed values.

An interesting sidelight to this study was the unusual multiplicity of methylene group (3.27-4.82 δ) which is attached to the nitrogen atom (N-2) in the ^{1}H-NMR spectra of cycloadducts. In compounds **35** (**a**,**b**,**d**,**e**,**f**,**i**) it appeared as multiplet, whereas in compounds **34** and **35** (**c**,**h**) methylene group showed up as a double doublet (J=16.2 Hz). In systems *viz.*, **34** and **35** (**l-n**) the methylene protons showed as a sharp singlet.

The anomalous behaviour of methylene protons suggested that when position-3 of the 1,2,4-oxadiazolidin-5-one system contains an aryl group, the rotation along the N_2-C bond becomes restricted and hence both protons become magnetically nonequivalent. Thus, initially expected splitting pattern for methylene protons (formed by the coupling of adjacent hydrogen atoms) get further coupled with the geminal hydrogen atoms, giving rise to a complex pattern.

On the basis of above analytical and spectral data a plausible mechanism of the reaction may be written as given in Scheme II.3.2.

The steric hindrance on the N-substituents of the oxaziridine and strong electrophilic nature of isocyanate group of CSI can cause a nucleophilic attack by the oxygen atom of oxaziridine ring. This generates a zwitterion **36**. The oxonium ion **36**, being a strained system, is highly unstable, and form a 1,5-dipolar species by the cleavage of the oxaziridine C-O bond and results in the formation of

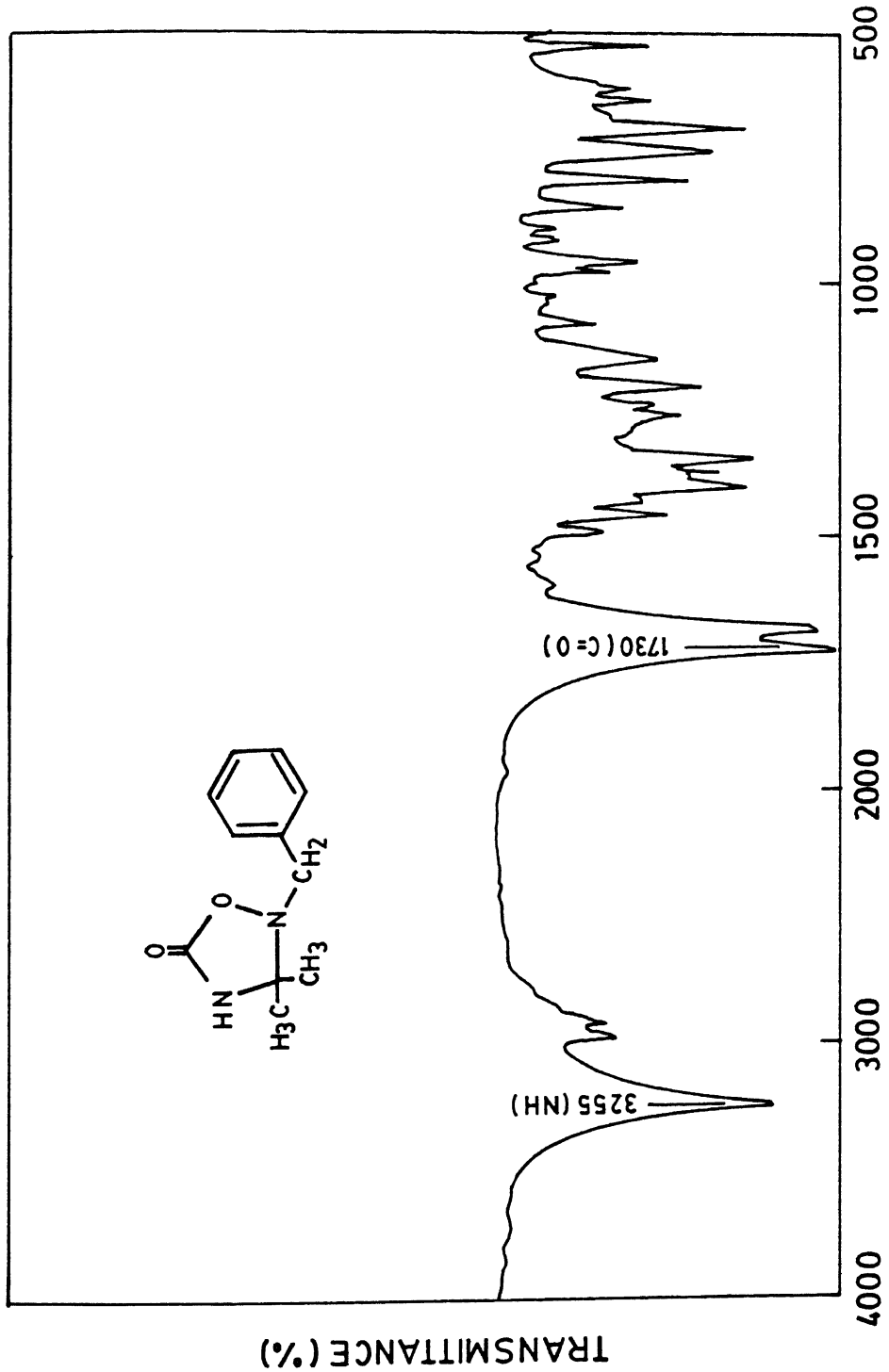


Fig. II.13 IR SPECTRUM OF 35L

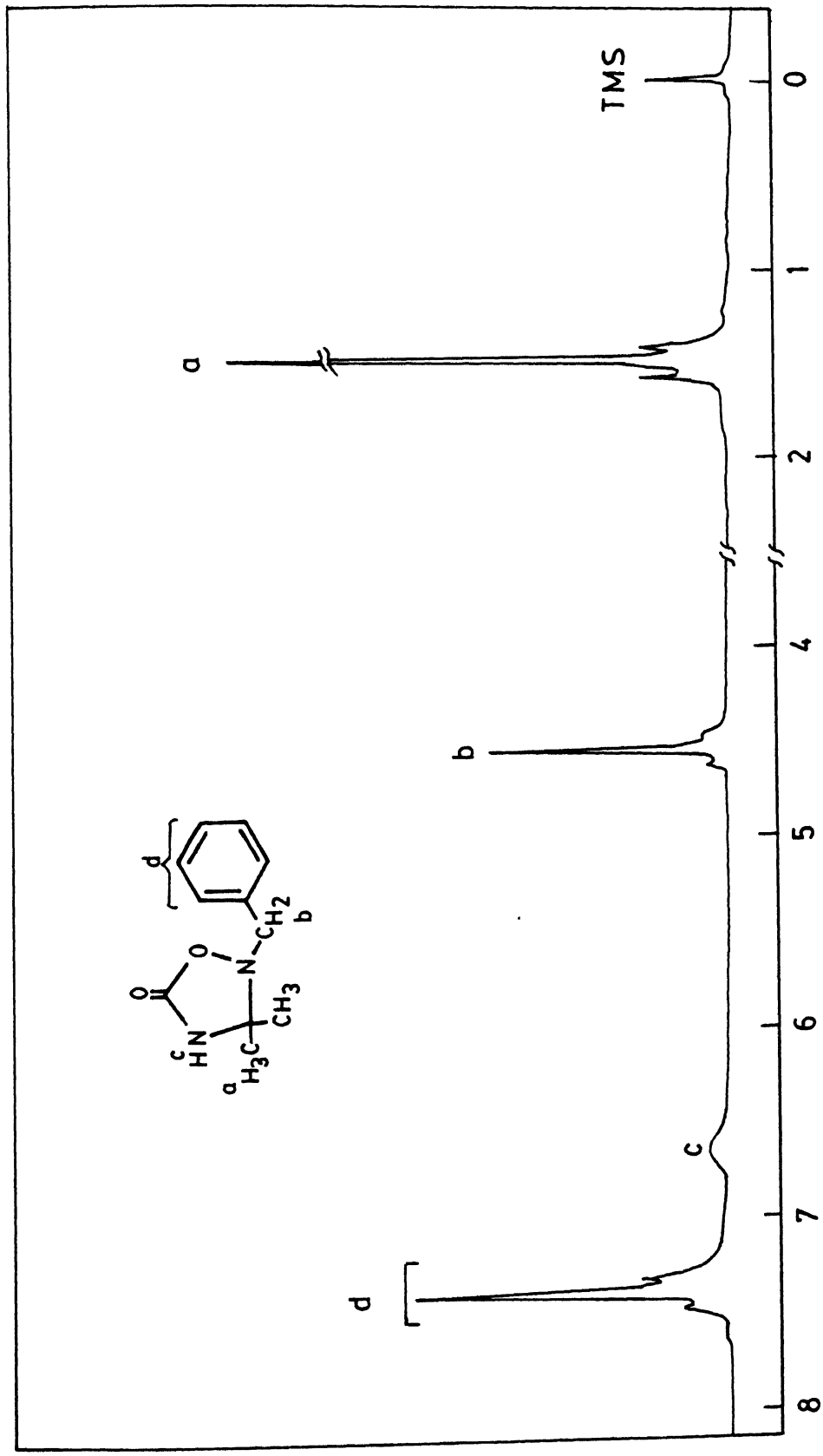


Fig. II·14 ^{1}H-NMR SPECTRUM OF 35l

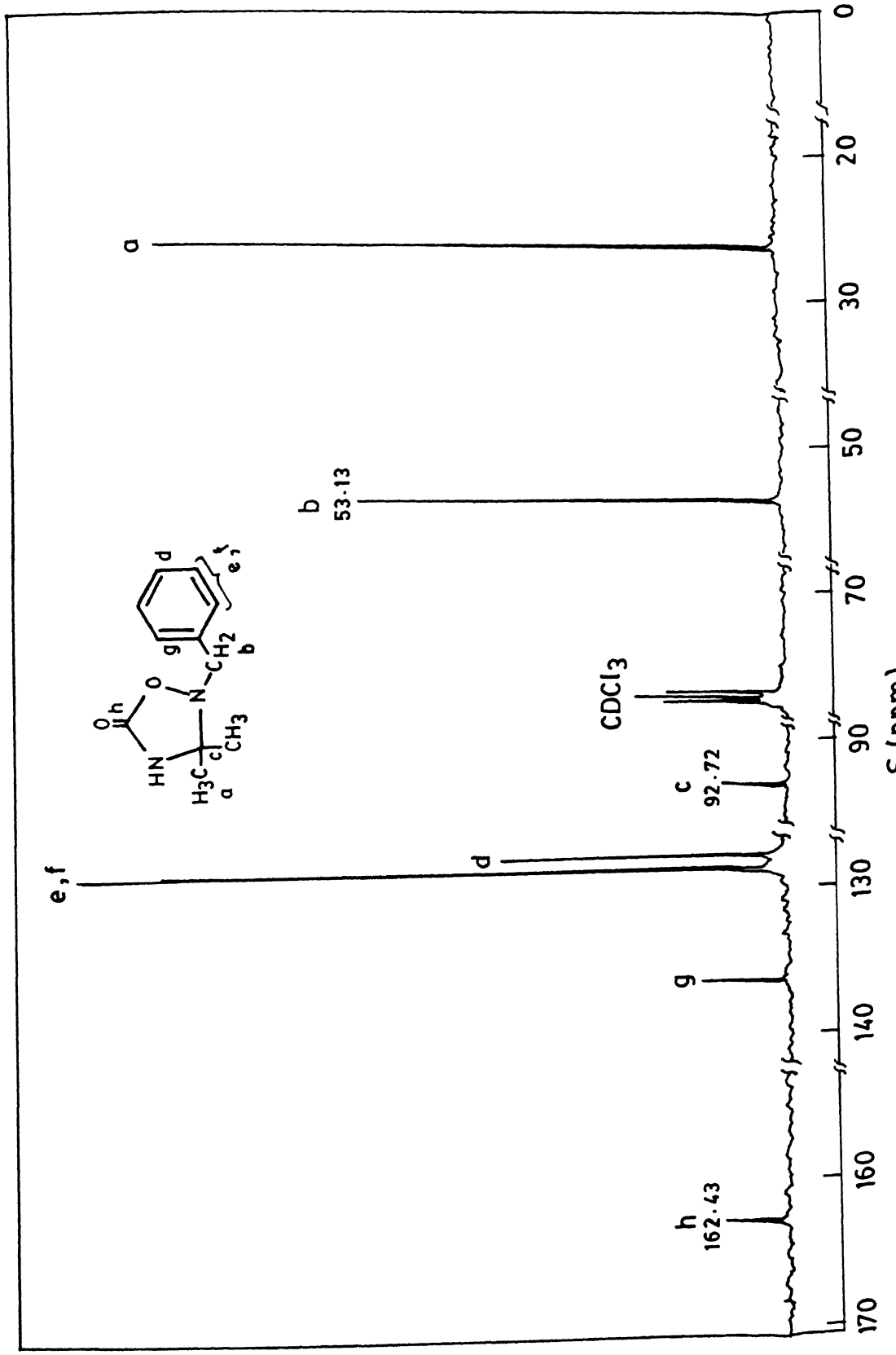


Fig. II·15 ^{13}C-NMR SPECTRUM OF 35l

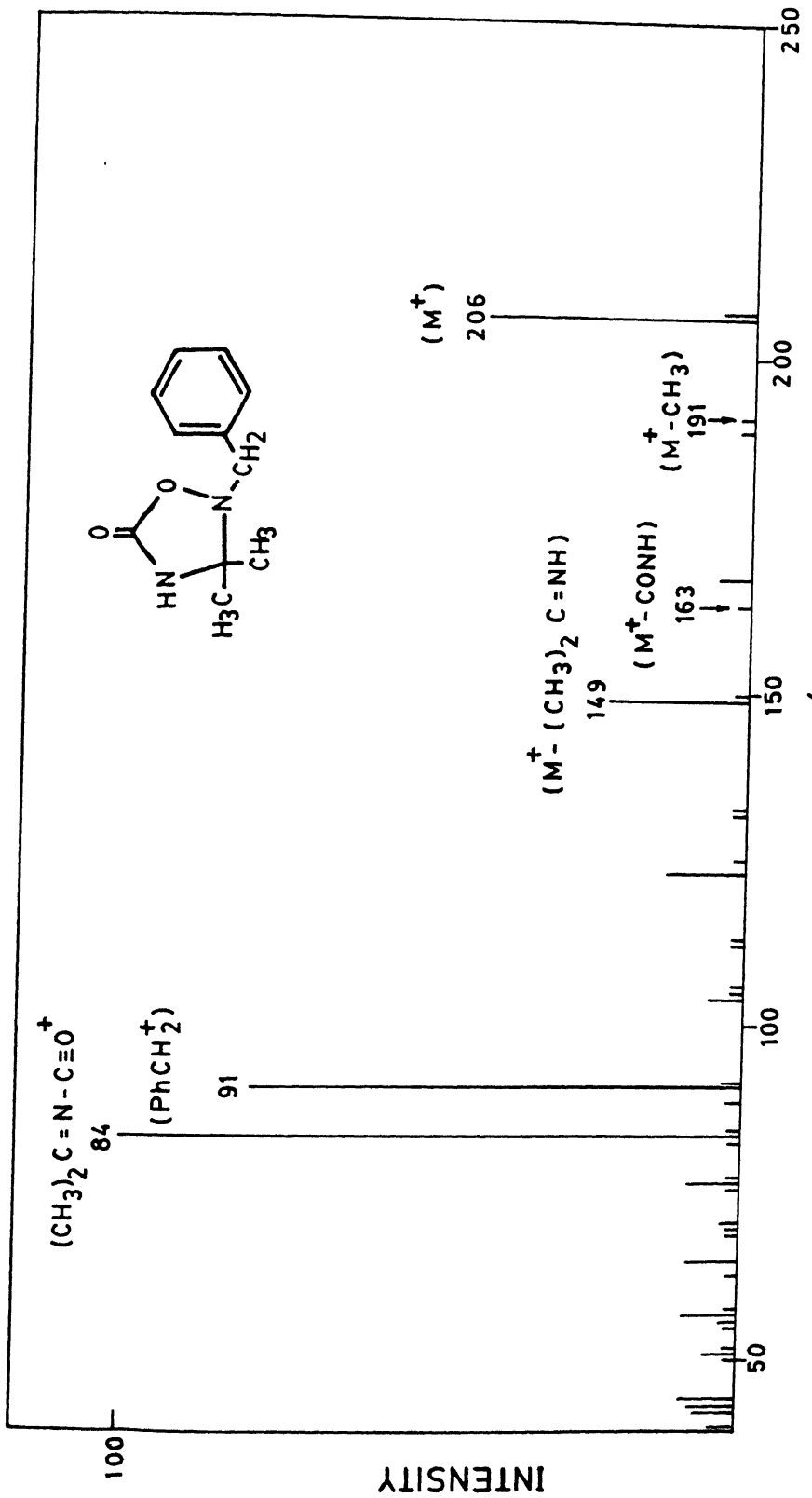
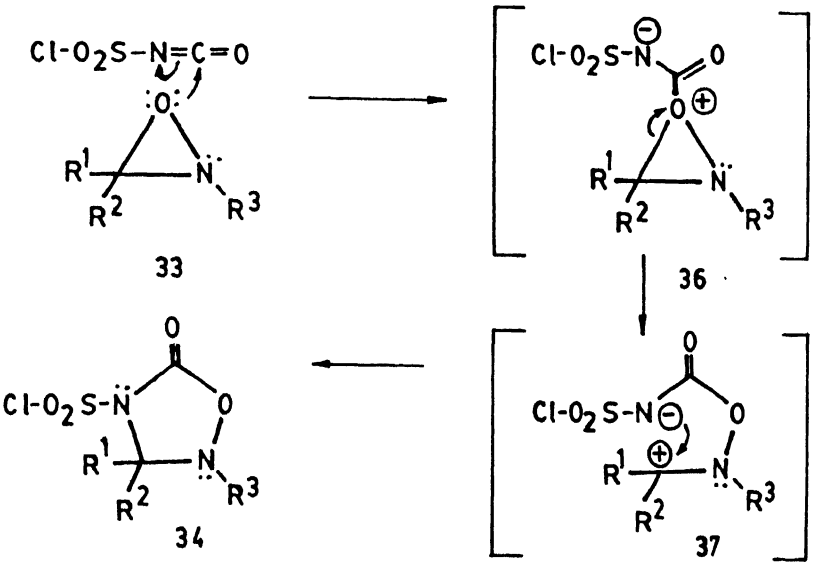


Fig. II.16 MASS SPECTRUM OF 351

SCHEME II.3·2



the transient carbocation 37. This intermediate cyclizes by the nucleophilic part of zwitterion to yield 1,2,4-oxadiazolidin-5-one. The aryl or dialkyl group on C-3 of the oxonium ion intermediate 36 can support the positive charge on the oxygen atom by sharing the charge density, which is further delocalised by the benzene ring. Hence, the nucleophilic attack by the nitrogen centre of zwitterion is directed on this carbon centre. The reaction is regiospecific and produces only one product 34.

II.4 EXPERIMENTAL

All melting points were determined on Fisher-Johns melting point apparatus and are uncorrected. The microanalysis were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyser. The IR spectra were recorded on Perkin-Elmer (580, 1320 or 1600) spectrophotometers using sodium chloride plates for liquids and

potassium bromide disks for solids. Mass spectra were taken on a Jeol (Model JMS D-300) mass spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on WP-80 (80 MHz, Brüker FT) and WM-400 (400 MHz Brüker FT) spectrometers. Proton and carbon (^{13}C) chemical shifts are reported in parts per million down field from internal reference TMS (δ). Multiplicity is indicated by the following abbreviations: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet) and brs (broadsinglet).

II.4.1 REAGENTS

Chlorosulfonyl isocyanate and *m*-chloroperbenzoic acid were purchased from Fluka, A.G., (Switzerland). Oxaziridines were prepared according the known procedures by using Schiff's bases and *m*-chloroperbenzoic acid. The purities of oxaziridines [active oxygen content (A.O.)] were determined by iodometry and were found to be more than 95%. Commercial grade solvents were distilled prior to use. Petroleum ether 40-60^{o}C was used. All the reactions were carried out in dry dichloromethane distilled from P_2O_5 and stored over molecular sieve-4A^{o}.

II.4.2 Preparation of Schiff's bases

The Schiff's bases employed as starting materials for the preparation of oxaziridines were prepared by condensation of the appropriate amines with aromatic aldehydes.[34-36] The water formed in the reaction being separated azeotropically using dry benzene. The formation of Schiff's base was identified with the help of strong absorption band at 1640-1670 cm^{-1} in the IR spectrum of the each compound.

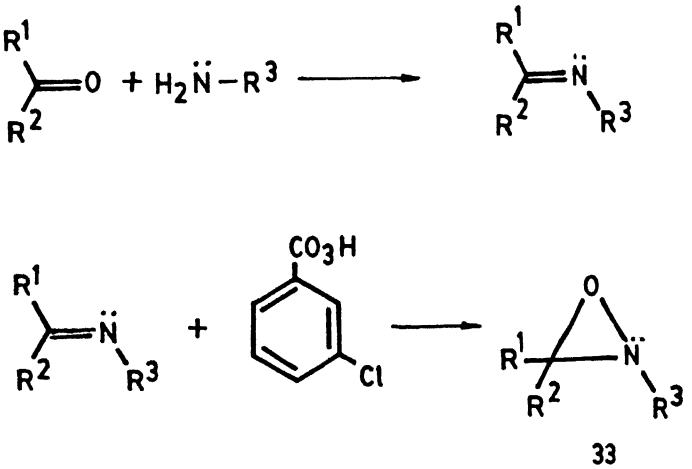
II.4.3 Preparation of 2-ethyl-3-phenyloxaziridine (33a)[37,39]

m-Chloroperbenzoic acid (3.8 g, 22 mmol) in dichloromethane (40 ml) was added slowly to a stirred solution of benzyledine-ethylamine (2.66 g, 20 mmol) in the same solvent (20 ml) at 5-10°C. The solution was stirred for 15 min and brought to room temperature. After 30 min the precipitated *m*-chlorobenzoic acid was filtered. The filtrate was washed with 5% sodium sulfite solution (10 ml), 5% sodium carbonate solution (10 ml) and dried over sodium carbonate. The solution was concentrated and the oxaziridine was purified by vacuum distillation.

Yield: 2.11 g (71%); b.p.: 75-78°C (0.2 mm). [Lit. 52°C (0.1 mm)].

Using the same procedure (*vide supra*) oxaziridines **33 (b-k)**[37,39] were prepared and purified by vacuum distillation or by column chromatography [Silica gel; petroleum ether-ethyl acetate (90:10)] (Scheme II.4.1; Table II.1).

SCHEME II.4.1



33

TABLE II.1

OXAZIRIDINES 33

33	Substituents			Yield (%)	b.p.°C(mm); [Lit. value]	Ref. No.
	R^1	R^2	R^3			
a	C_6H_5	H	C_2H_5	71	75-78(0.2); [52(0.1)]	37
b	C_6H_5	H	*n*-C_4H_9	64	78-80(0.5); [75(0.5)]	20
c	C_6H_5	H	$CH_2C_6H_5$	73	oil; [mp. 15-18]	37
d	*p*-$CH_3C_6H_4$	H	C_2H_5	62	80-85(0.3)	
e	*p*-$CH_3C_6H_4$	H	*n*-C_3H_7	69	oil	
f	*p*-$CH_3C_6H_4$	H	*n*-C_4H_9	76	85-87(0.5)	
g	*p*-$CH_3C_6H_4$	H	*t*-C_4H_9	72	68-70(0.5); [oil]	39
h	*p*-$CH_3C_6H_4$	H	$CH_2C_6H_5$	78	oil	
i	*p*-F-C_6H_4	H	C_2H_5	66	84-86(0.5)	
j	*p*-Cl-C_6H_4	H	*cy*-C_6H_{11}	70	semi-solid	
k	*p*-Br-C_6H_4	H	*cy*-C_6H_{11}	76	semi-solid	
l	CH_3	CH_3	$CH_2C_6H_5$	56	72-74(0.3); [71(0.3)]	38
m	CH_3	C_2H_5	$CH_2C_6H_5$	68	79-81(0.3)	
n	C_2H_5	C_2H_5	$CH_2C_6H_5$	59	72-75(0.4)	

Note: *cy*-C_6H_{11} = cyclohexyl

II.4.4 Preparation of 2-benzyl-3,3-dimethyloxaziridine (331)[38]

Benzylamine (2.14 g, 2.2 ml; 20 mmol), acetone (2.32 g, 3 ml; 40 mmol), dichloromethane (100 ml) and sodium carbonate (2.65 g, 25 mmol) were stirred overnight at room temperature. The mixture was cooled to 0°C and anhydrous solution of *m*-chloroperbenzoic acid (3.8 g; 22 mmol) in dichloromethane (50 ml) was added slowly. The resulting mixture was further stirred for 5h at the same temperature. The precipitated *m*-chlorobenzoic acid was filtered and the filtrate was washed successively with 5% sodium sulfide (10 ml), 5% sodium bicarbonate (10 ml) and dried over $MgSO_4$. The methylene chloride solution was concentrated in vacuum to a colorless oil. This oil was further purified by vacuum distillation.

Yield: 1.83 g (56%); b.p.: 72-74°C (0.3 mm). [Lit. 71°C (0.3 mm)].

Oxaziridines 33 (**m,n**) were prepared by employing the procedure as described above.

II.4.5 Reaction of 2-ethyl-3-phenyloxaziridine (33a) with CSI (General Method)

A solution of CSI (0.45 ml, 5 mmol) in dry dichloromethane (5 ml) was added dropwise to a magnetically stirred solution of oxaziridine **33a** (0.75 g, 5 mmol) in dichloromethane (15 ml) at 0°C for 10 min. The reaction mixture was stirred at the same temperature for 1h and then at room temperature (25°C) for 2h. The solvent was removed under diminished pressure and the viscous liquid was flash chromatographed over neutral alumina using ethyl acetate-petroleum ether (5:95) to furnish an oil (1.34 g). The oil was dissolved in minimum amount of dichloromethane and petroleum ether was added to it till it became turbid, and cooled overnight in a refrigerator.

Yield: 1.27 g (87%); m.p.: 64-65°C

Analytical and spectral data of 4-chlorosulfonyl-2-ethyl-3-phenyl--1,2,4-oxadiazolidin-5-one (34a)

Anal. for $C_{10}H_{11}ClN_2O_4S$: Calcd: C, 41.31; H, 3.81; N, 9.64 %
Found: C, 41.12; H, 3.87; N, 9.70 %

IR (KBr) ν_{max} : 1780, 1600, 1415, 1315, 1195, 765, 705 cm^{-1}

Mass m/z (rel. int.) : 292 (M^++2, 12), 290 (M^+, 22), 232 (3), 191 (3), 149 (36), 148 (55), 131 (86), 104 (35), 77 (100).

^{1}H-NMR ($CDCl_3$) δ : 1.31 (3H, t, J=7 Hz); 3.69 (2H, q, J=7 Hz), 6.33 (1H, s), 7.52 (5H, s).

^{13}C-NMR ($CDCl_3$) δ : 11.52, 43.90, 91.32, 128.26, 128.88, 132.52, 131.91, 151.80.

II.4.6 Hydrolysis of 4-chlorosulfonyl-2-ethyl-3-phenyl-1,2,4-oxadiazolidin-5-one (34a)

A solution of **34a** (0.44 g, 1.5 mmol) in ether (20 ml) was added slowly to a mixture of sodium sulfite (25%, 20 ml) and ether (20 ml) at 5°C. The mixture was stirred and the aqueous phase was kept slightly basic by the addition of aqueous potassium hydroxide (10%). Stirring was continued for 1h at room temperature. At the end of this period, reaction mixture was diluted with water (25 ml) and ether layer was separated. Aqueous layer was further extracted with ether (2x20 ml). Combined ethereal extracts were washed and dried (Na_2SO_4). Solvent was removed and the residue obtained was crystallized from dichloromethane-petroleum ether to yield **35a** in colorless needles.

Analytical and spectral data of 2-ethyl-3-phenyl-1,2,4-oxadiazolidin--5-one (35a)

Anal. for $C_{10}H_{12}N_2O_2$: Calcd: C, 62.48; H, 6.29; N, 14.57 %

: Found: C, 62.39; H, 6.38; N, 14.76 %

IR (KBr), ν_{max} : 3225, 1730, 1600, 1460, 1085, 995, 760, 700 $cm.^{-1}$

Mass, m/z (rel. int.) : 193 (M^++1, 34), 192 (M^+, 64), 149 (20), 132 (100), 105 (49), 104 (44).

^{1}H-NMR ($CDCl_3$), δ : 1.20 (3H, t), 3.47 (2H, m), 6.09 (1H, s), 6.75 (1H, brs), 7.47 (5H, m).

^{13}C-NMR ($CDCl_3$), δ : 11.49, 44.80, 86.60, 127.61, 128.71, 130.41, 135.36, 163.57.

II.4.7 Reaction of 2-*n*-butyl-3-phenyloxaziridine (33b) with CSI

Oxaziridine (33b) (0.89 g, 5 mmol) was reacted with CSI in an analogous manner as described in section II.4.5. Compound **34b** separated as a colorless oil by flash column chromatography (neutral alumina eluent: ethylacetate-petroleum ether, 10:90).

Yield: 1.39 g (87%); colorless oil

Analytical and spectral data of 2-*n*-butyl-4-chlorosulfonyl-3-phenyl--1,2,4-oxadizolidin-5-one (34b)

Anal. for $C_{12}H_{15}ClN_2O_4S$: Calcd: C, 45.21, H, 4.74, N, 8.79 %

Found: C, 45.03, H, 4.92, N, 8.68 %

IR (thin film) ν_{max} : 1770, 1595, 1420, 1195, 1020, 740, 690 $cm.^{-1}$

Mass m/z (rel. int.) : 319 (M^++1, 2), 318 (M^+, 3), 317 (M^+, 11), 219 (2) 203 (20), 176 (8), 131 (100), 104 (43).

^{1}H-NMR ($CDCl_3$) δ : 0.97 (t, 3H), 1.20-1.80 (m, 4H), 3.62 (m, 2H), 6.41 (s, 1H), 7.62 (s, 5H).

^{13}C-NMR ($CDCl_3$) δ : 13.76, 20.21, 29.02, 49.32, 91.39, 128.23, 128.87, 131.51, 131.93, 151.92

II.4.8 Hydrolysis of 2-*n*-butyl-4-chlorosulfonyl-3-phenyl-1,2,4-oxadiazolidin-5-one (34b)

Cycloadduct **34b** (0.32 g, 1.0 mmol) was hydrolysed according to the procedure described in section II.4.6. Product **35b** crystallized in colorless needles from dichloromethane-petroleum ether.

Yield: 0.14 g (63%); m.p.: 69-70°C

Analytical and spectral data of 2-butyl-3-phenyl-1,2,4-oxadiazolidin-5-one (35b)

Anal. for $C_{12}H_{16}N_2O_2$: Calcd: C, 65.43; H, 7.32; N, 12.72 %
Found: C, 65.50; H, 7.29; N, 12.78 %

IR (KBr) ν_{max} : 3180, 1710, 1600, 1450, 1210, 740, 690 $cm.^{-1}$

Mass m/z (rel. int.) : 220 (M^+, 4), 219 (M^+-1, 24), 177 (3), 176 (7), 132 (22), 131 (100), 104 (28).

^{1}H-NMR ($CDCl_3$) δ : 0.95, 1.23-1.80 (m, 4H), 3.41 (m, 2H), 6.11 (s, 1H), 6.95 (brs, 1H), 7.54 (s, 5H).

^{13}C-NMR ($CDCl_3$) δ : 13.16, 19.81, 28.74, 49.71, 86.67, 127.58, 128.65, 130.34, 135.36, 163.76.

II.4.9 Reaction of 2-benzyl-3-phenyloxaziridine (33c) with CSI

The reaction of **33c** (0.85 g, 4 mmol) with CSI (0.36 ml, 4 mmol) was carried out in an analogous manner as described in section II.4.5 and the reaction mixture was flash chromatographed over neutral alumina, using ethyl acetate-petroleum ether as eluent, to yield **34c**. Petroleum ether was added to the dichloromethane solution

of the compound, when colorless crystals of **34c** were obtained.

Yield: 1.29 g (91%); m.p.: 85°C.

Analytical and spectral data of 2-benzyl-4-chlorosulfonyl-3-phenyl-1,2,4-oxadiazolidin-5-one (34c)

Anal. for $C_{15}H_{13}ClN_2O_4S$: Calcd: C, 51.07; H, 3.71; N, 7.94 %
Found: C, 50.98; H, 3.77; N, 8.01 %

IR (KBr) ν_{max} : 1780, 1600, 1415, 1190, 1130, 755, 695 $cm.^{-1}$

Mass m/z (rel. int.) : 352 (M^+, 5), 351 (M^+-1, 4), 253 (9), 131 (58), 105 (31), 104 (33), 91 (9),90 (100).

^{1}H-NMR ($CDCl_3$) δ : 4.64 (d, 1H, J=16.2 Hz), 4.82 (d, 1H, J=16.2 Hz), 6.38 (s, 1H), 7.44 (s, 5H), 7.50 (s, 5H).

^{13}C-NMR ($CDCl_3$) δ : 52.71, 91.45, 128.29, 128.60, 128.76, 128.99, 129.06, 131.46, 131.77, 133.37, 151.77.

II.4.10 Hydrolysis of 2-benzyl-4-chlorosulfonyl-3-phenyl-1,2,4-oxadiazolidin-5-one (34c)

Compound **34c** (0.36 g, 1 mmol) was dissolved in acetone-water (20 ml, 9:1) and cooled to 0°C. Aqueous potassium hydroxide (10%) was added dropwise until the solution became neutral. The aqueous solution was stirred for 1h at 5-10°C and then diluted with water. The solution was extracted with dichloromethane (3x20 ml) and the combined extracts were washed with water, dried (Na_2SO_4) and evaporated in *vacuo* to furnish a white solid. It was recrystallized from petroleum ether-dichloromethane (1:2) as colorless crystals.

Yield: 0.19 g (73%), m.p.: 102°C.

Analytical and spectral data of 2-benzyl-3-phenyl-1,2,4-oxadiazolidin-5-one (35c)

Anal. for $C_{15}H_{14}N_2O_2$: Calcd: C, 70.85; H, 5.55; N, 11.02 %
Found: C, 70.53; H, 5.58; N, 11.09 %

IR (KBr) ν_{max} : 3200, 1705, 1600, 1440, 1150, 760, 700 $cm.^{-1}$

Mass m/z (rel. int.) : 254 (M^+, 11), 253 (M^+-1, 8), 211 (8), 132 (100), 91 (85).

^{1}H-NMR ($CDCl_3$) δ : 4.45 (d, 1H, J=16.2 Hz), 4.72 (d, 1H, J=16.2 Hz), 6.11 (s, 1H), 6.15 (brs, 1H), 7.41 (s, 5H), 7.50 (s, 5H).

^{13}C-NMR ($CDCl_3$) δ : 53.86, 86.89, 128.15, 128.46, 128.56, 128.89, 129.14, 131.63, 131.81, 133.21, 163.16.

II.4.11 Reaction of 2-ethyl-3-*p*-tolyloxaziridine (33d) with CSI

The reaction was carried out in the same manner, as described earlier (cf. section II.4.5), by using oxaziridine **33d** (0.66 g, 4 mmol) and CSI (0.36 ml, 4 mmol). The work-up of the reaction mixture in the usual way, furnished the product as an oil. The oil was in dichloromethane solution was diluted with petroleum ether when it separated as a solid, **34d**.

Yield: 1.06g (86%), m.p.: 71-72°C.

Analytical and spectral data of 2-ethyl-4-chlorosulfonyl-3-*p*-tolyl-1,2,4-oxadiazolidin-5-one (34d)

Anal. for $C_{11}H_{13}ClN_2O_4S$: Calcd: C, 43.35; H, 4.30; N, 9.19 %
Found: C, 43.07; H, 4.38; N, 9.34 %

IR (KBr) (ν_{max}) : 1780, 1615, 1420, 1210, 1000, 825 $cm.^{-1}$

Mass m/z (rel. int.) : 205 (M^+-SO_2Cl, 3), 204 (7), 163 (56), 162

(100), 145 (35), 133 (44), 118 (15), 104 (48).

^{1}H-NMR ($CDCL_3$) δ : 1.31 (t, 3H, J=6.3 Hz), 2.57 (s, 3H), 3.70 (q, 2H, J=6.3 Hz), 6.31 (s, 1H), 7.27 (d, 2H, J=7.5 Hz), 7.47 (d, 2H, J=7.5 Hz).

^{13}C-NMR ($CDCl_3$) δ : 11.40, 21.29, 43.77, 91.33, 128.18, 128.31, 12948, 141.83, 151.80.

II.4.12 Hydrolysis of 4-chlorosulfonyl-2-ethyl-3-*p*-tolyl-1,2,4-oxadiazolidin-5-one (34d)

Compound **34d** (0.46 g, 1.5 mmol) was hydrolysed as described in section II.4.6. Product **35d** obtained was recrystallized from ether-petroleum ether as colorless crystals.

Yield: 0.27 g (87%), m.p.: 122^{0}C.

Analytical and spectral data of 2-ethyl-3-*p*-tolyl-1,2,4-oxadiazolidin -5-one (35d)

Anal. for $C_{11}H_{14}N_2O_2$: Calcd: C, 64.06; H, 6.84; N, 13.58 %
Found: C, 63.97; H, 6.75; N, 13.65 %

IR (KBr) ν_{max} : 3205, 1730, 1610, 1435, 1000, 820 cm.$^{-1}$

Mass m/z (rel. int.) : 206 (M^+, 5), 205 (M^+-1, 19), 163 (3), 146 (100), 119 (9), 118 (7), 91 (12).

^{1}H-NMR ($CDCl_3$) δ : 1.17 (t, 3H, J=6.8 Hz), 3.34 (m, 2H), 6.12 (s, 1H), 6.45 (brs, 1H), 7.26 (d, 2H, J=8.0 Hz), 7.46 (d, 2H, J=8.0 Hz).

^{13}C-NMR ($CDCl_3$) δ : 11.42, 21.03, 44.76, 86.52, 127.63, 129.23, 132.36, 140.43, 163.23.

II.4.13 Reaction of 2-*n*-propyl-3-*p*-tolyloxaziridine (33e) with CSI

The reaction of **33e** (0.39 g, 2.2 mmol) with CSI (0.2 ml, 2.2 mmol) was carried out in an analogous manner as described in section II.4.5 and the reaction mixture was flash chromatographed [Neutral alumina, Petroleum ether-ethyl acetate (4:1)]. The N-chlorosulfonyl--1,2,4-oxadiazolidinone derivative **34e** was obtained as a colorless oil.

Yield: 0.57 g (81%).

Analytical and spectral data of 4-chlorosulfonyl-2-*n*-propyl-3-*p*-tolyl -1,2,4-oxadiazolidin-5-one (34e)

Anal. for $C_{12}H_{15}ClN_2O_4S$: Calcd: C, 45.21; H, 4.74; N, 8.79 %
Found: C, 45.13; H, 4.68; N, 8.83 %

IR (thin film) ν_{max} : 1770, 1610, 1425, 1200, 1020, 820 $cm.^{-1}$

Mass m/z (rel. int.) : 319 (M^++1, 3), 318 (M^+, 7), 219 (5), 217 (16), 177 (8), 145 (100), 118 (19).

^{1}H-NMR ($CDCl_3$) δ : 1.05 (t, 3H, J=7.0 Hz), 1.78 (m, 2H), 2.46 (s, 3H), 3.66 (m, 2H), 6.37 (s, 1H), 7.26 (d, 2H, J=8.0 Hz), 7.55 (d,2H, J=8.0).

^{13}C-NMR ($CDCl_3$) δ : 11.56, 20.08, 21.48, 52.16, 91.59, 127.96, 129.69, 133.32, 141.54, 151.48.

II.4.14 Hydrolysis of 4-chlorosulfonyl-2-*n*-propyl-3-*p*-tolyl-1,2,4--oxadiazolidin-5-one (34e)

Hydrolysis of **34e** (0.20g, 0.63 mmol) was effected by using the same procedure as described earlier (sec. II.4.6) yielded **35e**. The compound **35e** was purified by crystallisation from dichloromethane-petroleum ether.

Yield: 0.11g (79%); m.p.: 87°C.

Analytical and spectral data of 2-*n*-propyl-3-*p*-tolyl-1,2,4-oxadiazolidin-5-one (35e)

Anal. for $C_{12}H_{16}N_2O_2$: Calcd: C, 65.43; H, 7.32; N, 12.72 %
Found: C, 65.32; H, 7.38; N, 12.81 %

IR (KBr) ν_{max} : 3200, 1725, 1610, 1430, 1000, 825 $cm.^{-1}$

Mass m/z (rel. int.) : 220 (M^+, 63), 177 (3), 147 (49), 146 (100), 119 (46), 118 (37), 91 (70).

^{1}H-NMR ($CDCl_3$) δ : 0.96 (t, 3H, J=6.2 Hz), 1.69 (m, 2H), 2.41 (s, 3H), 3.39 (m, 2H), 6.01 (brs, 1H), 6.08 (s, 1H), 7.23 (d, 2H, J=8.0 Hz), 7.46 (d, 2H, J=8.0 Hz).

^{13}C-NMR ($CDCl_3$) δ : 11.13, 20.11, 21.23, 51.62, 86.57, 127.61, 129.37, 132.38, 140.59, 163.57.

II.4.15 Reaction of 2-*n*-butyl-3-*p*-tolyloxaziridine (33f) with CSI

Reaction of oxaziridine 33f (0.58 g, 3 mmol) with CSI (0.28 ml, 3 mmol) was carried out using the same procedure as described in section II.4.5. Elution of the alumina column with petroleum ether -ethyl acetate (4:1) furnished the product **34f** as colorless oil. Yield: 0.83 (82%).

Analytical and spectral data of 2-*n*-butyl-4-chlorosulfonyl-3-*p*-tolyl-1,2,4-oxadiazolidin-5-one (34f)

Anal. for $C_{13}H_{17}ClN_2O_4S$: Calcd: C, 46.91; H, 5.15; N, 8.42 %
Found: C, 47.78; H, 5.22; N, 5.38 %

IR (thin film) ν_{max} : 1765, 1610, 1420, 1195, 1020, 820 $cm.^{-1}$

Mass m/z (rel. int.) : 332 (M^+, 2), 233 (3), 191 (6), 190 (38), 146 (12), 145 (100), 118 (32), 105 (65), 91 (14).

^{1}H-NMR ($CDCl_3$) δ : 0.95 (t, 3H, J=6.5 Hz), 1.31-1.82 (m, 4H),

2.37 (s, 3H), 3.52 (m, 2H), 6.10 (s, 1H), 7.23 (d, 2H, J=8.1 Hz), 7.51 (d, 2H, J=8.1 Hz).

^{13}C-NMR ($CDCl_3$) δ : 13.81, 20.34, 21.28, 28.95, 49.52, 91.48, 128.26, 129.56, 132.42, 141.84, 151.36.

II.4.16 Hydrolysis of 2-*n*-butyl-4-chlorosulfonyl-3-*p*-tolyl-1,2,4-oxadiazolidin-5-one (34f)

Hydrolysis of **34f** (0.33g, 1 mmol) was carried out in a similar manner as described in section II.4.6, *i.e.* by using sodium sulfite and aqueous potassium hydroxide. The product **35f** crystallised from dichloromethane-petroleum ether in colorless needles.

Yield: 0.16 g (69%); m.p.: 79°C.

Analytical and spectral data of 2-*n*-butyl-3-*p*-tolyl-1,2,4-oxadiazolidin-5-one (35f)

Anal. for $C_{13}H_{18}N_2O_2$: Calcd: C, 66.64; H, 7.74; N, 11.96 %
Found: C, 66.35; H, 7.82; N, 11.92 %

IR (KBr) ν_{max} : 3205, 1720, 1610, 1430, 1230, 995, 826 cm^{-1}

Mass m/z (rel. int.) : 234 (M^+, 2), 147 (12), 146 (100), 119 (8), 118 (7), 105 (2), 91 (11).

^{1}H-NMR ($CDCl_3$) δ : 0.91 (t, 3H, J=6.5 Hz), 1.47-1.62 (m, 4H), 3.37 (m, 2H), 6.05 (s, 1H), 6.37 (brs, 1H), 7.20 (d, 2H, J=8.1 Hz), 7.44 (d, 2H, J=8.1 Hz).

^{13}C-NMR ($CDCl_3$) δ : 13.62, 19.62, 20.88, 28.48, 49.60, 85.70, 127.56, 129.11, 133.53, 139.73, 162.81.

II.4.17 Reaction of 2-*tert*-butyl-3-*p*-tolyloxaziridine (33g) with CSI

The procedure described in section II.4.5 for the preparation of the 1,2,4-oxadiazolidin-5-one **34g**, was followed by using oxaziridine **33g** (0.77 g, 4 mmol) and CSI (0.36 ml, 4 mmol). The crude product was purified by flash chromatography and subsequently crystallized from ether-petroleum ether to furnish the colorless crystals of **34g**.

Yield: 1.19 g (89%); m.p.: 81°C.

Analytical and spectral data of 2-*tert*-butyl-4-chlorosulfonyl-3-*p*-tolyl-1,2,4-oxadiazolidin-5-one (34g)

Anal. for $C_{13}H_{17}ClN_2O_4S$: Calcd: C, 46.91; H, 5.15; N, 8.42 %
Found: C, 46.82; H, 5.19; N, 8.49 %

IR (KBr) ν_{max} : 1760, 1610, 1420, 1200, 1100, 825 $cm.^{-1}$

Mass m/z (rel. int) : 332 (M^+, 2), 330 (9), 274 (7), 233 (2), 217 (17), 191 (4), 190 (12), 145 (89), 118 (79), 90 (75), 57 (100).

^{1}H-NMR ($CDCl_3$) δ : 1.50 (s, 9H), 2.32 (s, 3H), 6.10 (s, 1H), 7.26 (d, 2H, J=8.0 Hz), 7.36 (d, 2H, J=8.0 Hz).

^{13}C-NMR ($CDCl_3$) δ : 21.29, 26.34, 61.16, 90.58, 128.15, 129.43, 133.55, 141.67, 151.34.

II.4.18 Hydrolysis of 4-chlorosulfonyl-2-*tert*-butyl-3-*p*-tolyl-1,2,4-oxadiazolidin-5-one (34g)

Compound **34g** (0.4 g, 1.2 mmol) was hydrolysed according to the procedure described in section II.4.6. Product **35g** obtained was crystallized in colorless plates from dichloromethane-petroleum ether (5:1).

Yield: 0.33g (85%); m.p.: 181°C.

Analytical and spectral data of 2-*tert*-butyl-3-*p*-tolyl-1,2,4-oxadiazolidin-5-one (35g)

Anal. for $C_{13}H_{18}N_2O_2$: Calcd: C, 66.64; H, 7.74; N, 11.96 %
Found: C, 66.53; H, 7.79; N, 12.03 %

IR (KBr) ν_{max} : 3210, 1700, 1610, 1430, 1000, 820 $cm.^{-1}$

Mass m/z (rel. int.) : 234 (M^+, 3), 233 (M^+-1, 8), 146 (100), 119 (11), 91 (3), 57 (20).

^{1}H-NMR ($CDCl_3$) δ : 1.34 (s, 9H), 2.36 (s, 3H), 6.02 (s, 1H), 6.08 (brs, 1H), 7.22 (d, 2H, J=8.0 Hz), 7.46 (d, 2H, J=8.0 Hz).

^{13}C-NMR ($CDCl_3$) δ : 20.86, 26.06, 58.46, 85.01, 127.58, 129.05, 133.81, 139.61, 162.47.

II.4.19 Reaction of 2-benzyl-3-*p*-tolyloxaziridine (33h) with CSI

The reaction of **33h** (0.90 g, 4 mmol) with CSI (0.36 ml, 4 mmol) was carried out in a similar manner as described earlier (*vide supra*, section II.4.5). The product **34h** was crystallized with dichloromethane-petroleum ether as white crystalline solid.

Yield: 1.36 g (93%); m.p.: 90-91°C.

Analytical and spectral data of 2-benzyl-4-chlorosulfonyl-3-*p*-tolyl-1,2,4-oxadiazolidin-5-one (34h)

Anal. for $C_{16}H_{15}ClN_2O_4S$: Calcd: C, 52.39; H, 4.12; N, 7.64 %
Found: C, 52.26; H, 4.06; N, 7.81 %

IR (KBr) ν_{max} : 1760, 1595, 1410, 1190, 1170, 810, 740, 695 $cm.^{-1}$

Mass m/z (rel. int.) : 366 (M^+, 5), 365 (M^+-1, 3), 267 (2), 155 (54), 145 (39), 118 (20), 91 (12), 90 (100).

^{1}H-NMR ($CDCl_3$) δ : 2.35 (s, 3H), 4.61 (d, 1H, J=16.2 Hz), 4.83

(d, 1H, J=16.2 Hz), 6.28 (s, 1H), 7.11-7.52 (m, 9H).

^{13}C-NMR ($CDCl_3$) δ : 21.28, 52.60, 91.47, 127.75, 128.23, 128.48, 128.64, 128.76, 129.40, 129.60, 130.36, 134.35, 141.81, 151.84.

II.4.20 Hydrolysis of 2-benzyl-4-chlorosulfonyl-3-*p*-tolyl-1,2,4-oxadiazolidin-5-one (34h)

Compound **34h** (0.30 g, 0.8 mmol) was hydrolysed using acetone-water and dil. potassium hydroxide according to the procedure described in section II.4.10. Product **35h** thus obtained was crystallized from ethyl alcohol as colorless crystals.

Yield: 0.16 g (73%); m.p.: 138°C.

Analytical and spectral data of 2-benzyl-3-*p*-tolyl-1,2,4-oxadiazolidin-5-one (35h)

Anal. for $C_{16}H_{16}N_2O_2$: Calcd: C, 71.62; H, 6.01; N, 10.44 %
Found: C, 71.56; H, 6.09; N, 10.62 %

IR (KBr) ν_{max} : 3200, 1720, 1615, 1435, 1120, 815, 745, 700 $cm.^{-1}$

Mass m/z (rel. int.) : 268 (M^+, 4), 267 (M^+-1, 20), 224 (3), 146 (15), 145 (100), 118 (11), 91 (35).

^{1}H-NMR ($CDCl_3$) δ : 2.35 (s, 3H), 4.41 (d, 1H, J=15.4 Hz), 4.74 (d, 1H, J=15.4 Hz), 6.03 (s, 1H), 6.30 (brs, 1H), 7.14-7.48 (m, 9H).

^{13}C-NMR ($CDCl_3$) δ : 20.89, 53.69, 85.83, 127.61, 128.30, 128.63, 129.07, 133.39, 136.21, 139.81, 162.32.

II.4.21 Reaction of 2-ethyl-3-(4-fluorophenyl)oxaziridine (33i) with CSI

Oxaziridine **33i** (0.50 g, 3 mmol) was reacted with CSI (0.27 ml, 3 mmol) as described previously (*vide supra*, section II.4.5). The N-chlorosulfonyl adduct **34i** was obtained as colorless viscous oil. Trituration of the oil with ether-petroleum ether furnished the desired compound, **34i**, in colourless crystals.

Yield: 0.87 g (94%); m.p.: 74-75^{0}C.

Analytical and spectral data of 4-chlorosulfonyl-2-ethyl-3-(4-fluorophenyl)-1,2,4-oxadiazolidin-5-one (34i)

Anal. for $C_{10}H_{10}ClFN_2O_4S$: Calcd: C, 38.90; H, 3.27; N, 9.07 %
Found: C, 38.76; H, 3.22; N, 9.18 %

IR (thin film) ν_{max} : 1770, 1610, 1420, 1210, 1160, 840 cm.$^{-1}$

Mass m/z (rel. int.) : 308 (M^{+}, 3), 221 (11), 209 (4), 167 (18), 149 (100), 95 (34).

^{1}H-NMR ($CDCl_3$) δ : 1.32 (t, 3H, J=7.0 Hz), 3.62 (q, 2H, J=7.0 Hz), 6.23 (s, 1H), 6.93-7.63 (m, 4H).

^{13}C-NMR ($CDCl_3$) δ : 11.53, 43.96, 90.78, 115.43 (d, J=21.8 Hz, F-^{13}C), 129.43 (d, J=7.1 Hz, F-^{13}C), 132.41, 150.96, 163.46 (d, J=247.3 Hz).

II.4.22 Hydrolysis of 4-chlorosulfonyl-3-(4-fluorophenyl)-2-ethyl-1,2,4-oxadiazolidin-5-one (34i)

N-chlorosulfonyl derivative **34i** (0.5 g, 1.6 mmol) was hydrolysed in an usual manner (cf. section II.4.6). Product obtained was dissolved in dichloromethane and triturated with petroleum ether. On cooling white needles of **35i** were obtained.

Yield: 0.26 g (76%); m.p.: 96^{0}C.

Analytical and spectral data of 3-(4-fluorophenyl)-2-ethyl-1,2,4-oxadiazolidin-5-one (35i)

Anal. for $C_{10}H_{11}FN_2O_2$: Calcd: C, 57.14; H, 5.27; N, 13.37 %
Found: C, 57.10; H, 5.32; N, 13.46 %

IR (KBr) ν_{max} : 3180, 1730, 1605, 1230, 1130, 840, 760 $cm.^{-1}$

Mass m/z (rel. int.) : 211 (M^++1, 2), 210 (M^+, 13), 167 (2), 151 (9), 150 (100), 123 (12), 122 (13).

^{1}H-NMR (DMSO-D_6) δ : 1.15 (t, 3H, J=7.0 Hz), 3.27 (m, 2H,), 6.05 (s,1H), 6.80-7.45 (m, 4H), 8.21 (brs, 1).

^{13}C-NMR ($CDCl_3$) δ : 11.49, 44.78, 85.99, 115.79 (d, J=21.4 Hz F-^{13}C), 129.64 (d, J=6.6 Hz, F-^{13}C), 131.29, 164.00 (d, J=249.9 Hz, F-^{13}C), 163.54.

II.4.23 Reaction of 3-(4-chlorophenyl)-2-cyclohexyloxaziridine (33j) with CSI

The reaction of compound **33j** (1.19 g, 5 mmol) with CSI (0.45 ml, 5 mmol) was carried out in the usual manner (cf. section II.4.5). The reaction mixture was chromatographed (neutral alumina, ethyl acetate-petroleum ether (30:70)) to furnish **34j**. This on crystallization from dichloromethane gave colorless crystals.

Yield: 1.65 g (87%) m.p.: 130°C.

Analytical and spectral data of 3-(4-chlorophenyl)-4-chlorosulfonyl-2-cyclohexyl-1,2,4-oxadiazolidin-5-one (34j)

Anal. for $C_{14}H_{16}Cl_2N_2O_4S$: Calcd: C, 44.33; H, 4.25; N, 7.38 %
Found: C, 44.08; H, 4.30; N, 7.39 %

IR (KBr) ν_{max} : 1765, 1600, 1420, 1195, 1150, 1045, 995, 835 $cm.^{-1}$

Mass m/z (rel. int.) : 382 (M^++4, 5), 380 (M^++2, 21), 378 (M^+, 34),377 (1), 376 (19), 297 (6), 295 (10),

281 (1), 279 (2), 239 (8), 237 (15), 167 (22), 165 (82), 140 (8), 138 (18), 83 (100).

^{1}H-NMR ($CDCl_3$) δ : 1.02-2.31 (m, 10H), 3.76 (m, 1H), 6.30 (s, 1H), 7.46 (q, 4H).

^{13}C-NMR ($CDCl_3$) δ : 24.76, 24.97, 25.06, 28.44, 29.03, 58.58, 90.26, 129.02, 129.43, 130.71, 137.37, 150.59.

II.4.24 Hydrolysis of 3-(4-chlorophenyl)-4-chlorosulfonyl-2-cyclohexyl-1,2,4-oxadiazolidin-5-one (34j)

Adduct **34j** (0.5 g, 1.3 mmol) was hydrolysed with aqueous potassium hydroxide in aqueous acetone according to the procedure given in section II.4.10. Product, **35j** crystallized from ethanol in fine crystals.

Yield: 0.30 g (82%); m.p.: 169-170°C.

Analytical and spectral data of 3-(4-chlorophenyl)-2-cyclohexyl-1,2,4-oxadiazolidin-5-one (35j)

Anal. for $C_{14}H_{17}ClN_2O_2$: Calcd: C, 59.89; H, 6.10; N, 9.98 %
Found: C, 59.64; H, 6.23; N, 10.24 %

IR (KBr) ν_{max} : 3180, 1730, 1600, 1445, 1090, 995, 830 cm.$^{-1}$

Mass m/z (rel. int.) : 282 (M^++2, 3), 280 (M^+, 10), 237 (3), 168 (25), 166 (100), 150 (22), 138 (7), 83 (5).

^{1}H-NMR ($CDCl_3$) δ : 0.82-2.24 (m, 10H,) 3.66 (m, 1H), 6.11 (s, 1H), 6.58 (brs, 1H), 7.49 (q, 4H).

^{13}C-NMR ($CDCl_3$) δ : 25.27, 25.37, 25.66, 27.69, 29.81, 58.67, 86.09, 128.96, 129.06, 134.28, 136.41, 163.05.

II.4.25 Reaction of 3-(4-bromophenyl)-2-cyclohexyloxaziridine (33k) with CSI

Reaction of **33k** (0.85 g, 3 mmol) with CSI(0.27 ml, 3 mmol) was carried out as described earliar. The product **34k** obtained was crystallized from dichloromethane in light yellow crystals.

Yield: 1.17 g (92%); m.p.: 136°C.

Analytical and spectral data of 3-(4-bromophenyl)-4-chlorosulfonyl-2-cyclohexyl-1,2,4-oxadiazolin-5-one (34k)

Anal. for $C_{14}H_{16}BrClN_2O_4S$: Calcd: C, 39.68; H, 3.81; N, 6.61 %
Found: C, 39.81; H, 3.87; N, 6.67 %

IR (KBr) ν_{max} : 1760, 1595, 1425, 1200, 1155, 1050, 1010, 830 $cm.^{-1}$

Mass m/z (rel. int.) : 426(M^++4, 5), 424 (M^++2, 18), 422 (M^+ 11), 341 (20), 339 (15), 325 (5), 323 (6), 211 (77), 209 (84), 184 (12), 182 (15), 83 (100).

^{1}H-NMR ($CDCl_3$) δ : 0.95-2.30 (m, 10H), 3.84 (m, 1H), 6.35 (s, 1H), 7.39 (d,2H, J=8.3 Hz), 7.61 (d, 2H, J=8.3 Hz).

^{13}C-NMR ($CDCl_3$) δ : 24.93, 25.14, 25.20, 28.61, 29.21, 58.73, 90.47, 125.97, 129.74, 131.32, 132.20, 150.80.

II.4.27 Hydrolysis of 3-(4-bromophenyl)-4-chlorosulfonyl-2-cyclohexyl-1,2,4-oxadiadolidin-5-one (34k)

Compound **34k** (0.50 g, 1.18 mmol) on hydrolysis in the usual manner (*vide supra*, section II.4.6) furnished compound **35k**. Compound **35k** obtained was cryatallised from alcohol as pale yellow crystals.

Yield: 0.34g (89%); m.p.: 169°C.

Analytical and spectral data of 3-(4-bromophenyl)-2-cyclohexyl-1,2,4-oxadiazolidin-5-one (35k)

Anal. for $C_{14}H_{17}BrN_2O_2$: Calcd: C, 51.70; H, 5.27; N, 8.61 %
Found: C, 51.81; H, 5.30; N, 8.69 %

IR (KBr) ν_{max} : 3180, 1725, 1595, 1445, 1065, 995, 830 $cm.^{-1}$

Mass m/z (rel. int.) : 326 (M^++2, 11), 324 (M^+, 10), 283 (4), 281 (4), 212 (94), 210 (100), 184 (11), 182 (12), 150 (34), 83 (5).

^{1}H-NMR ($CDCl_3$) δ : 0.82-2.14 (m, 10H), 3.60 (m, 1H), 6.08 (s, 1H), 7.09 (brs, 1H), 7.41 (d,2H, J=8.5 Hz), 7.62 (d,2H, J=8.5 Hz).

^{13}H-NMR ($CDCl_3$) δ : 25.24, 25.34, 25.63, 27.66, 29.76, 58.65, 86.11, 124.63, 129.28, 131.90, 134.76, 163.00.

II.4.27 Reaction of 2-benzyl-3,3-dimethyloxaziridine (331) with CSI

Oxaziridine 331 (0.82 g, 5 mmol) was reacted with CSI (0.45 ml, 5 mmol) in an analogous manner as described in section II.4.5. The product 341 was separated by flash column chromatography [neutral alumina-petroleum ether-ethyl acetate, (80:20)] as a colorless oil.

Yield: 0.87 g.

Analytical and spectral data of 2-benzyl-4-chlorosulfonyl-3,3-dimethyl-1,2,4-oxadiazolidin-5-one (341)

Anal. for $C_{11}H_{13}ClN_2O_4S$: Calcd: C, 43.35; H, 4.30; N, 9.19 %
Found: C, 43.31; H, 4.67; N, 9.48 %

IR (thin film) ν_{max} : 1760, 1595, 1410, 1380, 1170, 1035, 735, 695 $cm.^{-1}$

Mass m/z (rel. int.) : 306 (M^++2, 5), 304 (M^+, 15), 269 (1), 206

(2), 105 (13), 91 (100), 84 (56).

^{1}H-NMR ($CDCl_3$) δ : 1.42 (s, 6H), 4.42 (s, 2H), 7.25 (s, 5H).

^{13}C-NMR ($CDCl_3$) δ : 23.75, 51.85, 99.38, 128.23, 128.61, 133.71, 151.74.

II.4.28 Hydrolysis of 2-benzyl-4-chlorosulfonyl-3,3-dimethyl-1,2,4-oxadiazolidin-5-one (341)

Adduct **341** (0.61 g, 2 mmol) was hydrolysed according to the procedure described in section II.4.6. Reaction mixture was subjected to column chromatography (neutral alumina, petroleum ether ethyl acetate (60:40)) to furnish a colorless oil. This oil was dissolved in ether and diluted with petroleum ether till the turbidity was apparent and was left overnight in a refrigerator. Compound **351** was found to separate in colorless crystals.

Yield: 0.27 g (65%) m.p.: 86^{0}C.

Analytical and spectral data of 2-benzyl-3,3-dimethyl-1,2,4-oxadiazolidin-5-one (351)

Anal. for $C_{11}H_{14}N_2O_2$: Calcd: C, 64.06; H, 6.84; N, 13.58 %
Found: C, 64.12; H, 6.91; N, 13.52 %

IR (KBr) ν_{max} : 3255, 1730, 1690, 1495, 1370, 1145, 745, 700 cm.$^{-1}$

Mass m/z (rel. int.) : 206 (M^+, 45), 191 (2), 189 (6), 163 (4), 149 (25), 91 (79), 84 (100).

^{1}H-NMR ($CDCl_3$) δ : 1.40 (s, 6H), 4.52 (s, 2H), 6.64 (brs, 1H), 7.33 (s, 5H).

^{13}C-NMR ($CDCl_3$) δ : 26.62, 53.13, 92.72, 128.30, 128.45, 135.98, 162.43.

II.4.29 Reaction of 2-benzyl-3-ethyl-3-methyloxazirindine (33m) with CSI

Reaction of oxaziridine **33m** (0.71 g, 4 mmol) was carried out with CSI (0.36 ml, 4 mmol) in an analogous manner as described in section II.4.5. The product **34m** was obtained, by flash column chromatography, as colorless oil.

Yield: 0.79 g (62%).

Analytical and spectral data of 2-benzyl-4-chlorosulfonyl-3-ethyl-3-methyl-1,2,4-oxadiazolidin-5-one (34m)

Anal. for $C_{12}H_{15}ClN_2O_4S$: Calcd: C, 45.21; H, 4.74; N, 8.79 %
Found: C, 45.04; H, 4.87; H, 8.92 %

IR (thin film) ν_{max} : 1760, 1590, 1405, 1185, 1030, 740, 695 $cm.^{-1}$

Mass m/z (rel. int.) : 320 (M^++2, 4), 318 (M^+, 11), 305 (3), 303 (8), 283 (3), 220 (4), 119 (5), 98 (32), 91 (100).

^{1}H-NMR ($CDCl_3$) δ : 0.89 (t, 3H, J=7.0 Hz), 1.73 (s, 3H), 2.13 (q, 2H, J=7.0 Hz), 4.60 (s, 2H), 7.21 (s, 5H).

^{13}C-NMR ($CDCl_3$) δ : 7.32, 22.78, 28.54, 51.88, 104.68, 128.58, 128.89, 134.28, 151.52.

II.4.30 Hydrolysis of 2-benzyl-4-chlorosulfonyl-3-ethyl-3-methyl-1,2,4-oxadiazolidin-5-one (34m)

Compound **34m** (0.48 g, 1.5 mmol) was hydrolysed according to the procedure described previously (cf. section II.4.28). Product **35m** obtained from column chromatography was crystallised from ether-petroleum ether as colorless crystals.

Hz), 4.64 (s, 2H), 7.34 (s, 5H).

^{13}C-NMR ($CDCl_3$) δ : 7.31, 28.10, 51.98, 104.87, 128.38, 128.54, 128.63, 133.81, 151.93.

II.4.32 Hydrolysis of 2-benzyl-4-chlorosulfonyl-3,3-diethyl-1,2,4-oxadiazolidin-5-one (34n)

Cycloadduct **34n** (0.50g, 1.5 mmol) was hydrolysed using sodium sulfite and base, according to the method given in section II.4.28. Product **35n** was obtained by column chromatography. It was further purified by crystallization (ether-petroleum ether) and separated in colorless crystals.

Yield: 0.21 g (60%); m.p.: 68°C.

Analytical and spectral data of 2-benzyl-3,3-diethyl-1,2,4-oxadiazolidin-5-one (35n)

Anal. for $C_{13}H_{18}N_2O_2$: Calcd: C, 66.64; H, 7.74; N, 11.96 %
Found: C, 66.43; H, 7.89; N, 12.12 %

IR (KBr) ν_{max} : 3210, 1730, 1685, 1490, 1125, 750, 700 $cm.^{-1}$

Mass m/z (rel. int.) : 234 (M^+, 49), 217 (4), 205 (3), 191 (5), 149 (2), 112 (100), 91 (92).

^{1}H-NMR ($CDCl_3$) δ : 0.88 (t, 6H, J=6.7 Hz), 1.72 (q, 4H, J=6.7 Hz), 4.55 (s, 2H), 6.20 (brs, 1H), 7.36 (s, 5H).

^{13}C-NMR ($CDCl_3$) δ : 7.56, 32.28, 52.76, 94.76, 127.98, 128.46, 128.69, 134.26, 162.29.

REFERENCES

1. (a) H. Krimm, *British Patent*, 743, 940, 1956; *Chem. Abstr.*, 1957, **51**, 3656f.
   (b) H. Krimm, *Chem. Ber.*, 1958, **91**, 1057.
2. (a) W.D. Emmons, *J. Am. Chem. Soc.*, 1956, **78**, 6208.
   (b) W.D. Emmons, *J. Am. Chem. Soc.*, 1957, **79**, 5739.
3. F.A. Davis, R.H. Jenkins Jr., *Asymmetric Synthesis*, J.D. Morrison, Ed., Academic Press, Vol. **4**, Chap. 4, 1984, pp. 313-353.
4. (a) E. Schmidz, *Adv. In Heterocycl. Chem.*, 1963, **2**, 83.
   (b) E. Schmidz, *Adv. In Heterocycl. Chem.*, 1979, **24**, 63.
5. E. Schmidz, *Comprehensive Heterocyclic Chemistry*, W. Lwowski Ed., Pergamon Press, Vol.7, Chap. 5, 1984, pp. 195-236.
6. F.A. Davis, A.C. Sheppard, *Tetrahedron*, 1989, **45**, 5703.
7. S. Andreae, E. Schmitz, *Synthesis*, 1991, 327.
8. (a) Y. Hata, M. Watanabe, *J. Org. Chem.*, 1981, **46**, 610.
   (b) Y. Hata, M. Watanabe, *J. Am. Chem. Soc.*, 1979, **101**, 6671.
9. (a) W.H. Pirkle, P.L. Rinaldi, *J. Org. Chem.*, 1977, **42**, 3217.
   (b) W.H. Pirkle, P.L. Rinaldi, *J. Am. Chem. Soc.*, 1977, **99**, 3510.
10. Y. Gao, R.M. Hanson, J.M. Klunder, S.Y.Ko, H. Masamune K.B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765.
11. F.A. Davis, R.T. Reddy, W. Han, P.J. Carroll, *J. Am. Chem. Soc.*, 1992, **114**, 1428.
12. A.I. Meyers and K. Higashiyama, *J. Org. Chem.*, 1987, **52**, 4592.
13. E.J. Corey, M.C. Kang, M.C. Desai, A.K. Ghosh, I.N. Houpis, J.

14. F.A. Davis, R.T. Reddy, J.P. McCauley Jr., R.M. Przeslawski, M.E. Harakal, *J. Org. Chem.*, 1991, 56, 809.

15. J.S. Splitter, T.M. Su, H. Ono, M. Calvin, *J. Am. Chem. Soc.*, 1971, 93, 4075.

16. S.P. Joseph, D.N. Dhar, *Tetrahedron*, 1986, **42**, 5979.

17. S.P. Joseph, D.N. Dhar, *Tetrahedron*, 1988, **44**, 5209.

18. A.M.T. Bell, J. Bridges, R. Cross, C.P. Falshaw, B.F. Taylor, G.A. Taylor, I.C. Whittaker, M.J. Begley, *J. Chem. Soc., Perkin Trans. I*, 1987, 2593.

19. A. Nour-El-Din, *J. Chem. Res*, 1984, (S), 325; (M), 3019.

20. M. Komatsu, Y. Ohshiro, H. Hotta, M-a. Sato and T. Agawa, *J. Org. Chem.*, 1974, 39, 948.

21. M. Komatsu, Y. Ohshiro, K. Yasuda, S. Ichijima, T. Agawa, *J. Org. Chem.*, 1974, 39, 957.

22. M. Komatsu, Y. Ohshiro, T. Agawa, M. Kuriyama, N. Yasuoka, N. Kasai, *J. Org. Chem.*, 1986, **51**, 407.

23. N. Murai, M. Komatsu, Y. Ohshiro, T. Agawa, *J. Org. Chem.*, 1977, **42**, 448.

24. B.A. O'Brien, W.Y. Lam, D.D. DesMarteau, *J. Org. Chem.*, 1986, **51**, 4466.

25. A. Padwa, K.F. Koehler, *Heterocycles*, 1986, **24**, 611.

26. F. Toda, K. Tanaka, *Chem. Lett.*, 1987, 2283.

27. A. Lattes, E. Oliveros, M. Rivière, C. Belzecki, D. Mostowicz, W. Abramskj, C. Piccinni.-Leopardi, G. Germain, M.V. Meerssche, *J. Am. Chem. Soc.*, 1982, **104**, 3929.

28. E. Oliveros, M. Rivière, J.P. Malrieu, Ch. Teichteil, *J. Am. Chem. Soc.*, 1979, **101**, 318.

29. E. Oliveros, M. Rivièri, A. Lattes, *J. Heterocycl. Chem.*, 1980,

30. F.A. Davis, J.M. Billmers, D.J. Gosciniak, J.C. Towson, R.D. Bach, *J. Org. Chem.*, 1986, **51**, 4240.

31. F.A. Davis, R.T. Reddy, W. Han, P.J. Carroll, *J. Am. Chem. Soc.*, 1992, **114**, 1428.

32. F.A. Davis, N.F. Abdul-Malik, S.B. Awad, M.E. Harakal, *Tetrahedron Lett.*, 1981, 917.

33. F.A. Davis, M.E. Harakal, S.B. Awad, *J. Am. Chem. Soc.*, 1983, **105**, 3123.

34. N.H. Cormbell, R.D. Babson, C.E. Harris, *J. Am. Chem. Soc.*, 1943, **65**, 312.

35. D.G. Norton, V.E. Haury, F.C. Davis, L.J. Mitchell, S.A. Ballard, *J. Org. Chem.*, 1954, **19**, 1054.

36. G. Hilgetag, A. Martini, Ed., "*Preparative Organic Chemistry*" John Wiley & Sons, 1972, p. 506.

37. R.G. Pews, *J. Org. Chem.*, 1967, **32**, 1628,

38. D. St. C. Black, N.A. Blackman, *Aust. J. Chem.*, 1975, **28**, 2547.

39. K. Kloc, E. Kubicz, J. Młochowski, L. Syper, *Synthesis*, 1987, 1084.

CHAPTER III

REACTION OF CHLOROSULFONYL ISOCYANATE WITH 1-AROYLAZIRIDINES

III.1 ABSTRACT

Reaction of some 1-aroylaziridines with chlorosulfonyl isocyanate have been studied in detail. The aroylaziridines chosen for the present study include: 1-Benzoyl-2,2-dimethylaziridine (**45a**), 1-(4-bromobenzoyl)-2,2-dimethylaziridine (**45b**), 1-(4-methylbenzoyl)--2,2-dimethylaziridine (**45c**), 1-(3-chlorobenzoyl)-2,2-dimethylaziridine (**45d**), 1-(4-chlorobenzoyl)-2,2-dimethylaziridine (**45e**), 1-(4-*tert*-butylbenzoyl)-2,2-dimethylaziridine (**45f**), 1-(4-methoxybenzoyl)-2,2-dimethylaziridine (**45g**), 1-[2-(5-bromofuroyl)]-2,2--dimethylaziridine (**45h**) and 1-(4-nitrobenzoyl)-2,2-dimethylaziridine (**45i**). With the exception of 1-(4-nitrobenzoyl)-2,2-dimethylaziridine (**45i**), all other 1-aroylaziridines underwent a facile reaction with CSI, followed by hydrolysis, to furnish two compounds *viz.*, 2-oxazolines* **48(a-h)** and 2-imidazolidinones **50(a-h)** derivatives. However, 1-(4-nitrobenzoyl)-2,2-dimethylaziridine reacts with CSI to yield 2-oxazoline derivative **48i** as the sole product. The products **48** and **50** have been identified on the basis of analytical and spectral evidences. A plausible mechanism (*vide infra*, Scheme III.3.2) involving a seven membered intermediate **47** has been advanced to explain the formation of 2-oxazoline **48(a-i)** and 2-imidazolidinone **50(a-h)**.

* Note - The IUPAC name = 4,5-Dihydrooxazole

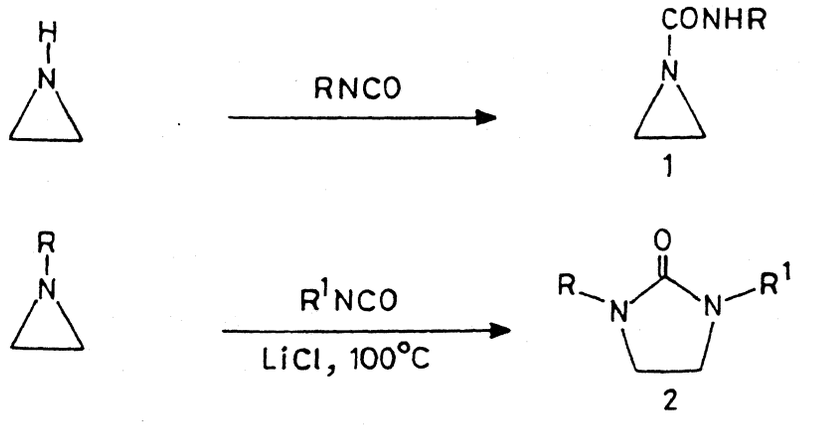
III.2 INTRODUCTION

We have studied the reaction of CSI with 1-aroylaziridines, in connection with our on-going research programme on the reactivity of three membered heterocycles (*vide supra*, chapter II) with CSI and forms the subject matter of this chapter. These aziridines contain a highly strained three membered ring systems (for example, oxaziridines and oxiranes) hence they are susceptible to ring cleavage by heterocumulenes and acidic reagents. It was, therefore, interesting to study the reaction of 1-aroylaziridines with chlorosulfonyl isocyanate.

Since the discovery of aziridines in 1888 by Gabriel[1], the chemistry of aziridines has been developing rapidly.[2-5] They undergo a variety of reactions including several ring transformations and photochemical reactions.[6] A few examples cited in literature are relevant to our present work and are reported here.

The reaction of unsubstituted aziridines with isocyanates, lead to the formation of the corresponding urea[7] derivatives **1**. The lithium chloride catalyzed reactions of N-substituted aziridines with alkyl, acyl, aryl, aroyl and sulfonyl isocyanates, at elevated temperature (>100°C), however, give 1,3-disubstituted 2-imidazolidones[8] **2** (Scheme III.2.1).

SCHEME III.2.1



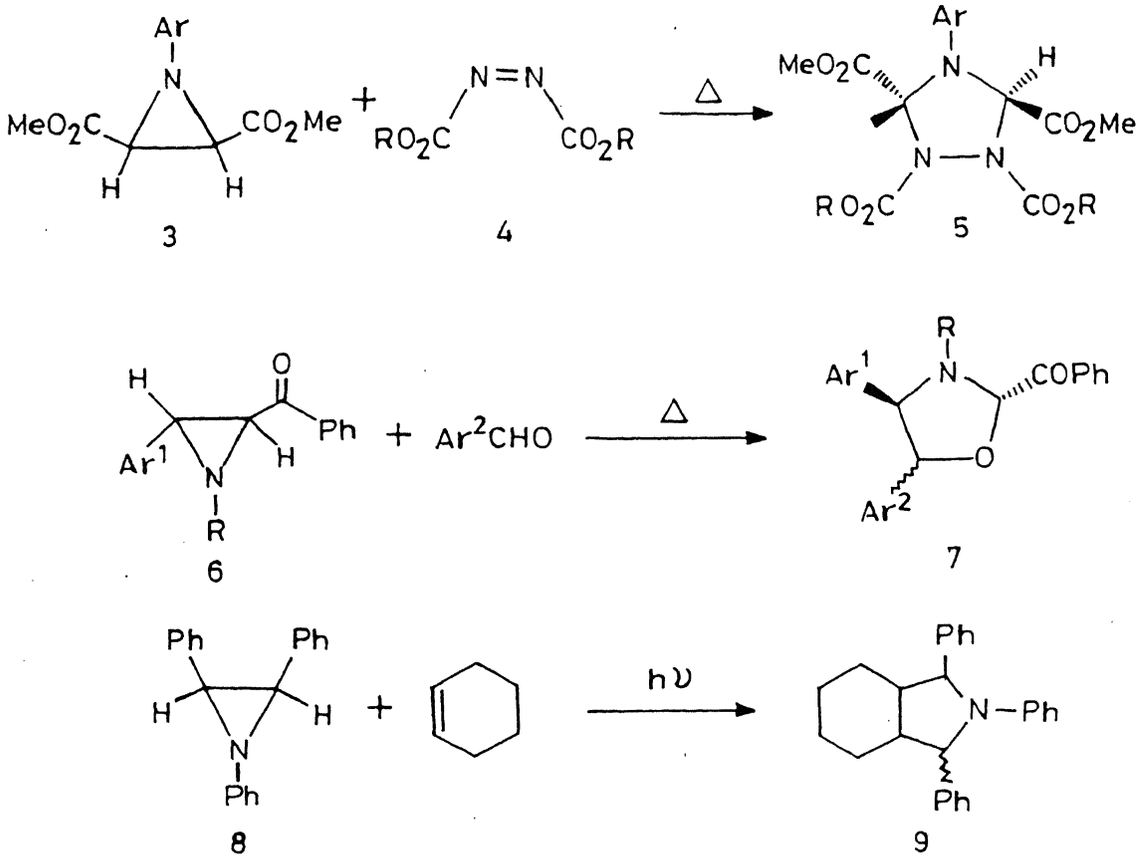
Dipolar cycloaddition reactions of aziridines are of synthetic importance and the synthetic application of these reactions have been reviewed.[9] Cycloaddition reactions of aziridines with a wide range of dipolarophiles have been studied. These reactions proceed *via* intermediate azomethine ylides,[10] formed from aziridines either thermally or photochemically. The reaction of dialkyl azodicarboxylates (**4**) with the *cis*-aziridine **3** is stereospecific to give the *trans*-products[11] **5**. The high reactivity of azomethine ylides formed from 2-aroylaziridines (**6**), allow the addition of aromatic aldehydes to give oxazolidines **7**. The mechanism of reaction involves the 1,3-dipolar addition of *trans*-azomethine ylide[12] (formed by the thermal cleavage of aziridine **6** to the aromatic aldehyde.

Under the photochemical conditions *cis*-1,2,3-triphenyl-aziridines (**8**) reacts with cyclohexene[13] to furnish a pair of stereoisomeric 1,2,3-triphenyloctahydroisoindole (**9**). The reaction involves the photolysis of C-C bond of aziridine ring system. Cycloaddition reactions of aziridines and 2-aroylaziridines are highlighted in Scheme III.2.2.

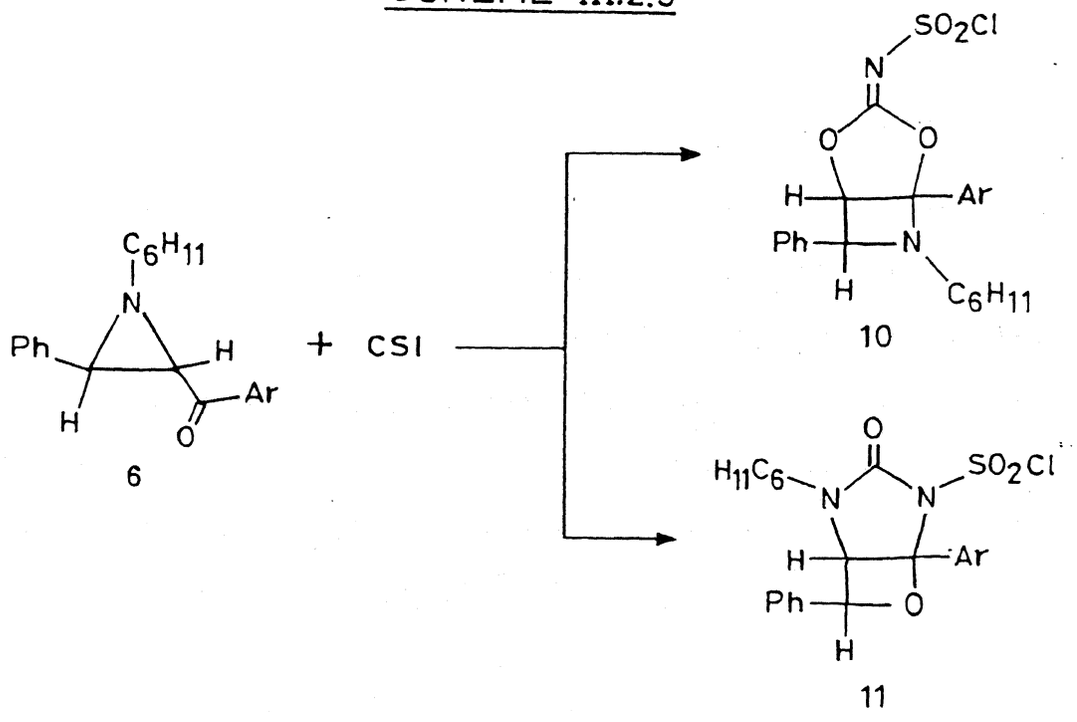
As already discussed (*vide supra*, Section I.3.2) N-alkyl or aryl substituted *cis*-aziridines, such as, *cis*-1,2,3-triphenyl-aziridine[14] reacts with chlorosulfonyl isocyanate in a facile manner to produce N-chlorosulfonylimino-1,3-oxazolidines. Similarly, *cis*-1-cyclohexyl-2-aroyl-3-phenylaziridines derivative react with CSI to give the corresponding N-chlorosulfonylimino-1,3-oxazolidine derivatives. These adducts can be hydrolyzed to the corresponding oxazolidine-2-ones. On the other hand, the *trans*-1-cyclohexyl--2-aroyl-3-phenylaziridines[14] (**6**) react with CSI to give bicyclic fused heterocycles **10**, **11** (Scheme III.2.3). The formation of

heterocycles **10**, **11** involves the intramolecular participation of aroyl group of aziridine **6** in cycloaddition.

SCHEME III.2.2

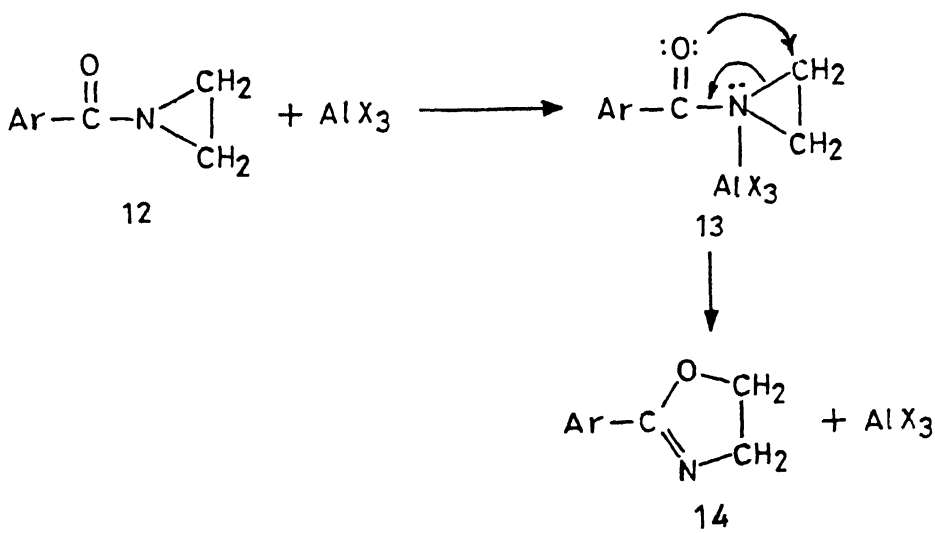


SCHEME III.2.3



It is reported that N-acylaziridines **12** undergo isomerization to 2-oxazolines **14** in the presence of an acidic catalyst, such as, mineral acids or Lewis acids ($AlCl_3$ or $AlBr_3$). The mechanism[15] for the isomerization involves the addition of the lone pair of amido nitrogen to Lewis acid catalyst to form a complex **13**. This is followed by the cleavage of C-N bond of the aziridine ring and subsequent intramolecular cyclization by the oxygen to form the oxazolinium salt. The catalyst is regenerated at the end of reaction

SCHEME III.2.4



Activated aziridine ring systems are susceptible towards the ring opening, by a variety of nucleophilic reagents. Most of the aziridines, which undergo direct nucleophilic ring opening, possess strong electron accepting group *viz.*, RCO, RSO_2, CN, Ar *etc.* on the nitrogen atom. Thus, 1-aroyl-2,2-dialkylaziridines undergo isomerization, in high yields, to 2-aryl-4,4-dialkyl-2-oxazoline (**15**) in the presence of iodide ions.[16,17]

The reaction of O-alkylaziridinecarbamate with aniline[18] has been reported to produce ethyl-N-(β-anilinoethyl)carbamate (16). Similarly, trityl sodium (a comparatively strong base) reacts with ethyl aziridinecarbamate to give the corresponding ethylcarbamate 17.

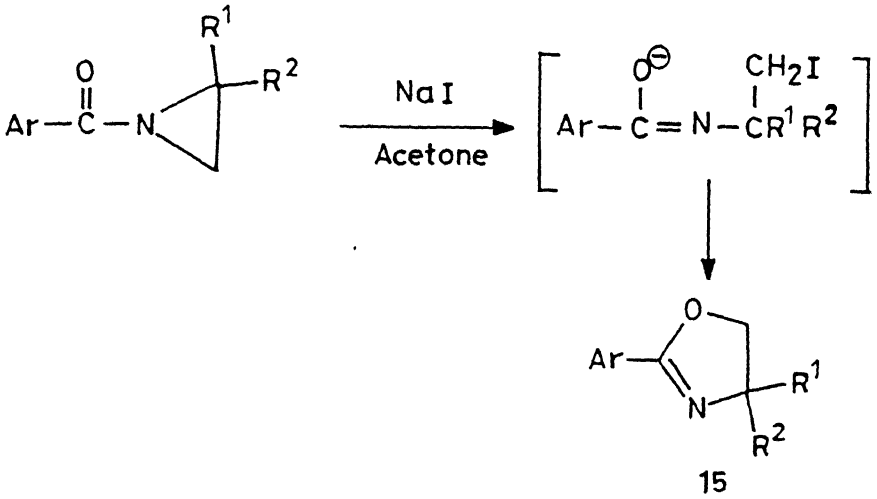
The most useful reactions of activated aziridines are with carbanion nucleophiles. For example, the addition of malonate salt[19] with activated aziridines typifies the ring expanded heterocycle 18. Ring opening reactions of 1-acylaziridines which are initiated by nucleophilic reagents are shown in Scheme III.2.5.

Ring opening reactions of aziridines are greatly accelerated in acidic media (Scheme III.2.6). N-acylaziridines[15,17] as well as their sulfur analogues undergo ring cleavage in the presence of acid catalysts *viz.*, $AlCl_3$, HCl, H_2SO_4, H_3PO_4 and Ph_3P *etc.* to yield the rearranged products 2-oxazoline 20 and 2-thiazoline 19 respectively.

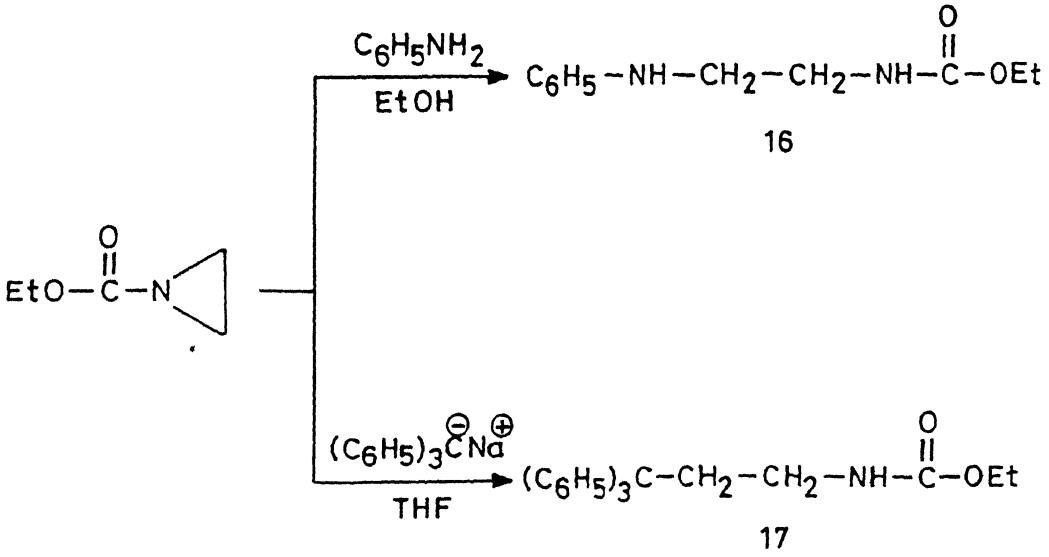
N-Acylaziridines undergo reaction with triphenylphosphine to yield a ylide. This ylide (prepared *in situ*) undergoes a subsequent Wittig reaction with an aromatic aldehyde to furnish α-substituted primary allylic amines[20] 21.

Only a limited number of reactions of 1-aroylaziridines with dipolar species are reported. These reactions involve the cleavage of aziridine ring by dipolar species, namely, enamines,[21] phosphonium ylides[22] and nitrones. Nitrones 22 are 1,3-dipolar species and undergo a (3+3) cycloaddition reaction with 1-aroylaziridines[23] to produce a cycloadduct *viz.*, 4-aroyltetrahydro-2H-1,2,4-oxadiazines (24) and an isomerized product 2-aryl-2-oxazoline (25). A mechanism that could account for the formation of both 1,2,4-oxadiazines and 2-aryl-2-oxazolines involves a nucleophilic attack of the nitrone oxygen on the aziridinyl carbon to form the dipolar intermediate 23.

SCHEME III.2.5

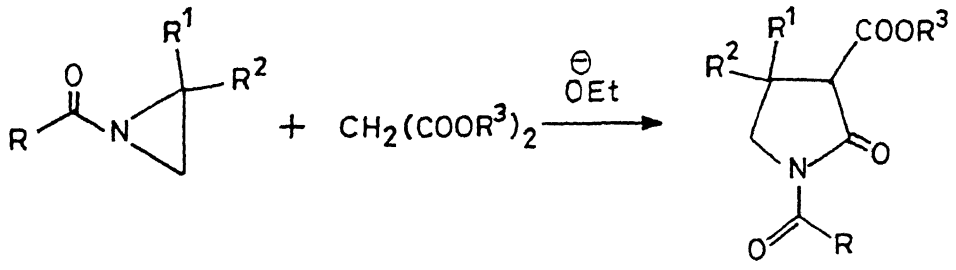


15



16

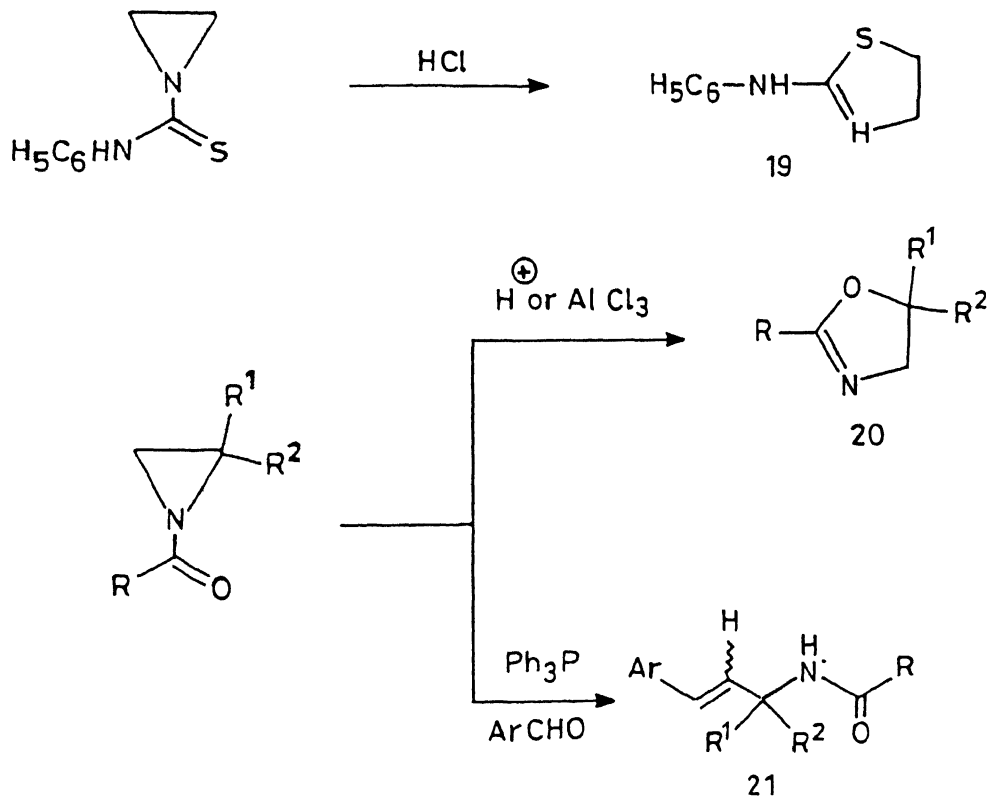
17



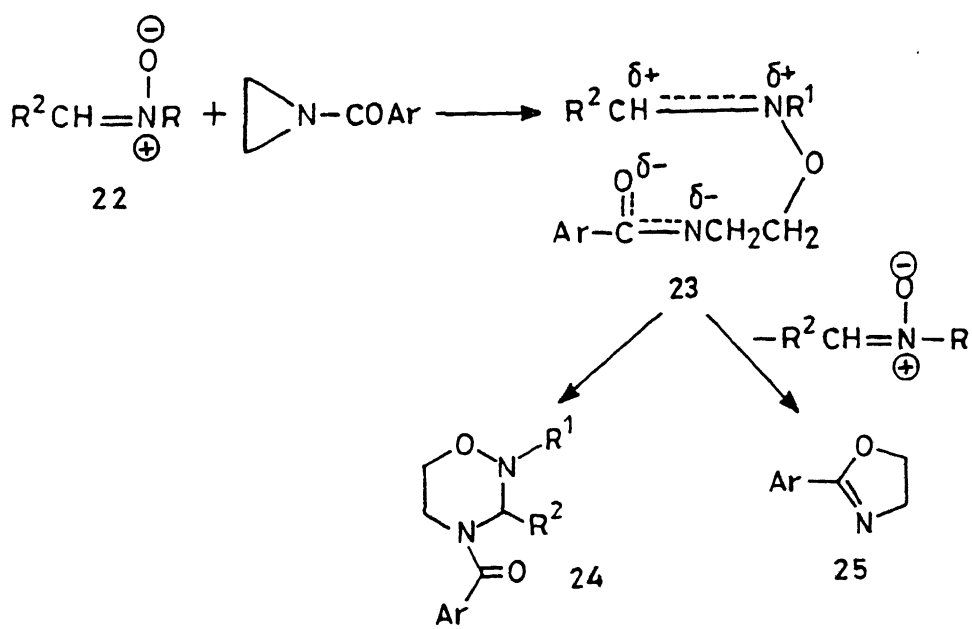
18

The intermediate 23 cyclizes to give cycloadduct 24 or eliminates nitrone to give the isomeric 2-oxazoline 25 as depicted in Scheme III.2.7.

SCHEME III.2.6

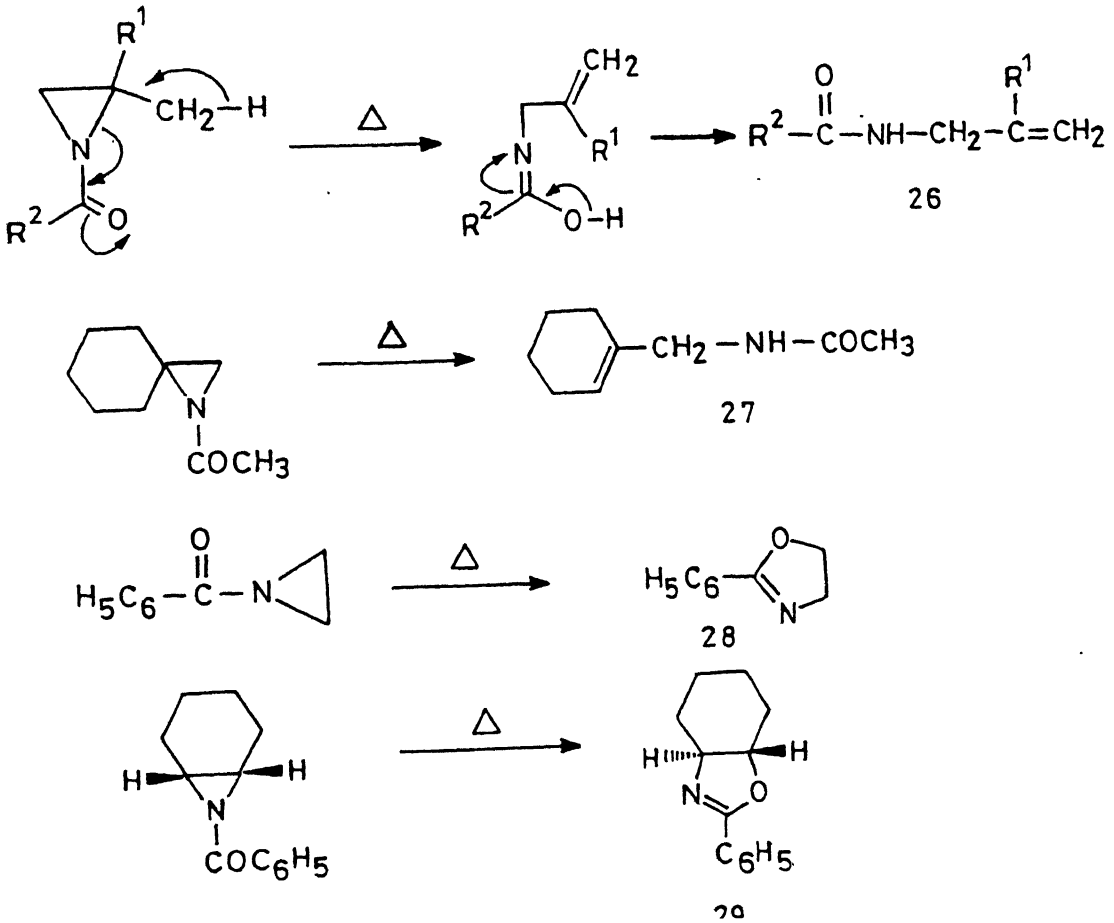


SCHEME III.2.7



Aziridines bearing acyl group on nitrogen atom of the three membered ring also display interesting thermal chemistry (Scheme III.2.8). Fanta and Deutsch[24] have reported the pyrrolytic isomerization of 1-acyl-2-alkylaziridines to unsaturated amide. Thus, 1-acetyl-2,2-dimethylaziridine undergo pyrrolytic rearrangement to N-(β-methallyl)acetamide (26). Similarly, 7-acetyl-azaspiro[5.2]-octane[25] upon heating rearranged to N-(1-cyclohexenylmethyl)acetamide (27). This thermal isomerization of N-acylaziridine involves the intramolecular attack by the lone pair of the carbonyl oxygen at the ring carbon to cause the rupture of the aziridine ring. N-Benzoylaziridine and N-benzoyl-*cis*-cyclohexenimine under pyrrolytic conditions gave 2-phenyl-2-oxazoline (28) and *trans*-2-phenyl-4,5--tetramethylene-2-oxazolidine[26] (29) respectively.

SCHEME III.2.8



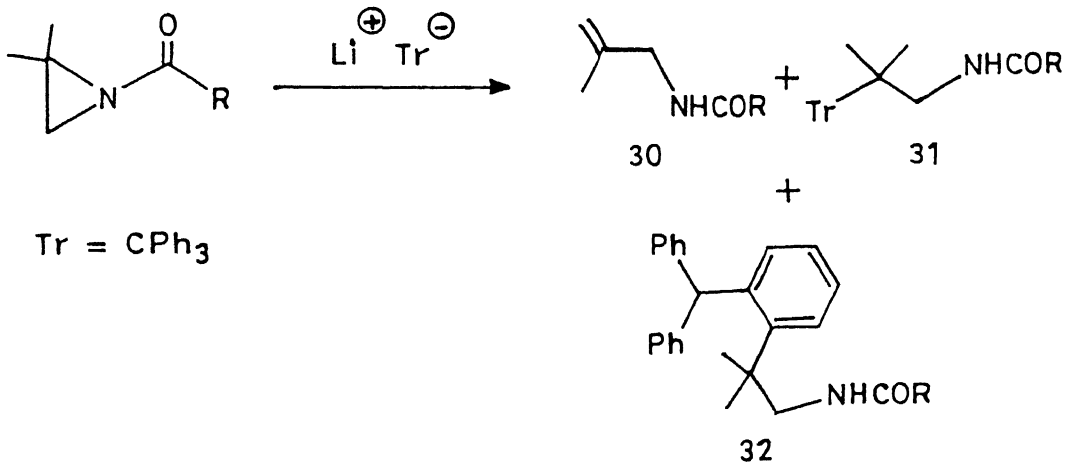
Reductive ring opening reactions of 1-acylaziridines with radicals (obtained from trityl anion, anthracene hydride, tri-*n*-butyl tinhydride) are known in literature. Single electron transfer reaction between trityl anion[27] and 1-acylaziridines provide the methallyl amides and the triphenylmethanes.

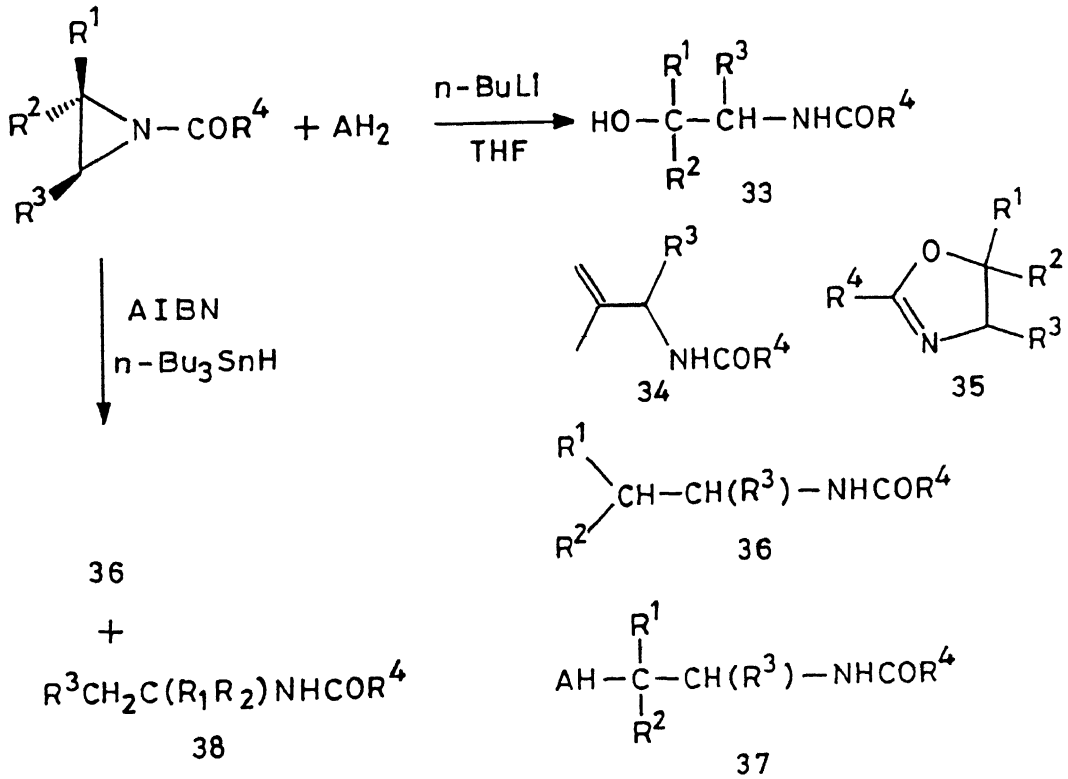
Anthracene hydride[28] (AH^-) reacts with N-acylaziridines by reductive opening of the aziridine ring. Thus, the N-aroylaziridines afforded high yields of N-alkylamides **33**,**34** and **36** including some minor products like amidoethyl derivatives of AH_2 (9,10-dihydro-anthracene) **37** and 2-oxazoline **35**.

Reaction of N-acylaziridines with an excess of tri-*n*-butyl tinhydride[29] and azobisisobutyronitrile (AIBN), as catalyst, in refluxing benzene provided the products **36** and **38**. The reaction did not proceed in absence of AIBN. The dependence of reductive ring opening on AIBN is a proof for a radical chain process. Radical reactions of 1-acylaziridines are shown in Scheme III.2.9.

From the above cited reactions of 1-aroylaziridines, it is apparent that the cleavage of aziridine ring and the participation of carbonyl group were involved during the course of reaction. In presence of Lewis acid 1-aroylaziridines isomerized to 2-oxazoline (*vide supra*, Scheme III.2.4). 1-aroyl-2,2-dimethylaziridines are activated systems and may form 1,5-dipolar species in the presence of Lewis acid. As already reported, CSI undergoes 1,5-dipolar cycloaddition with vinyl oxiranes.[30] Therefore, it was thought interesting to study the reaction of 1-aroyl-2,2-dimethylaziridines with the heterocumulene, CSI. The basic aim was to know whether 1-aroylaziridine (**45**) gives a seven membered heterocycle (*via* 1,5-dipolar addition) or a usual five membered heterocycle, which was

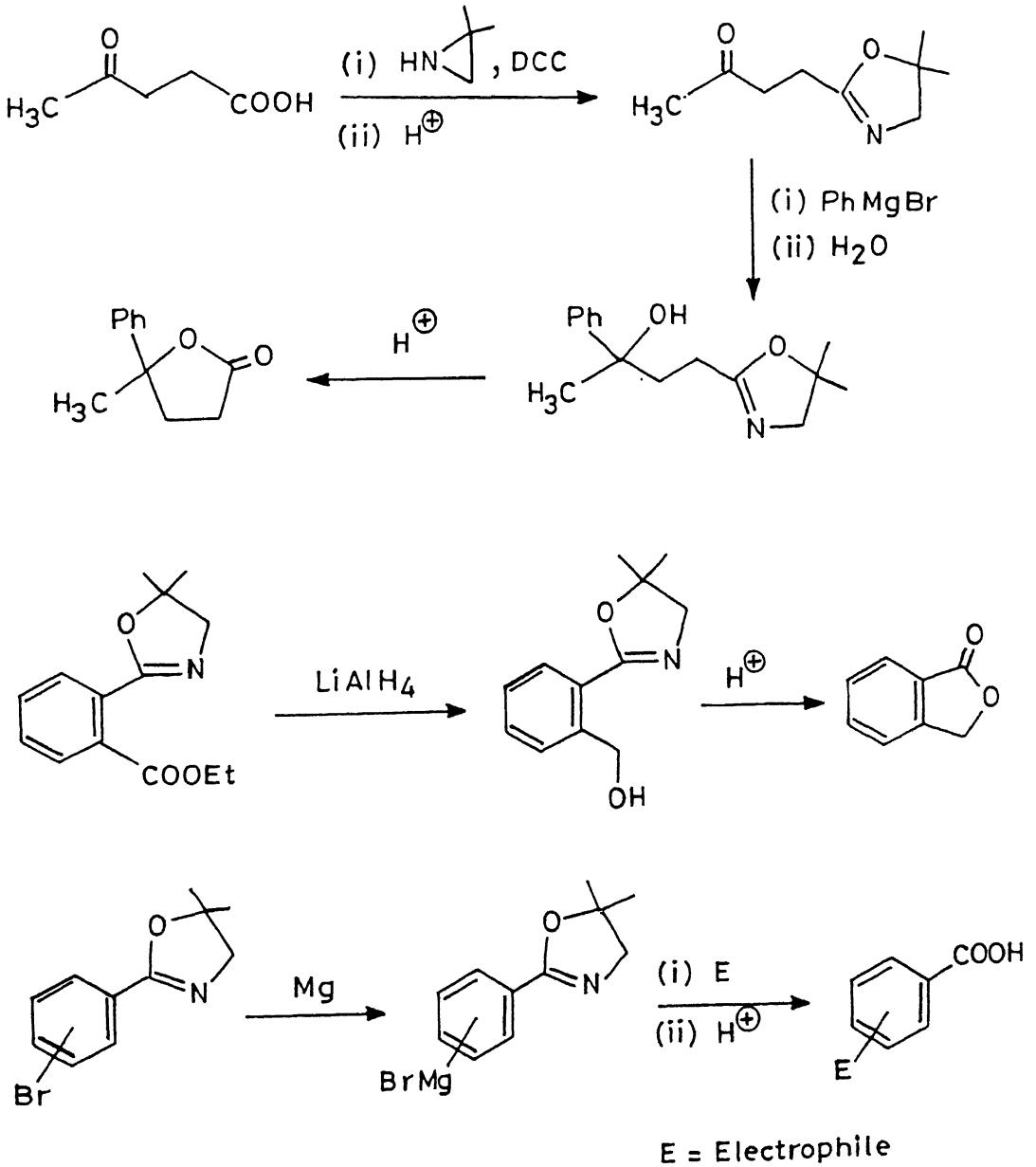
SCHEME III.2.9





formed by the previously reported reaction of aziridine and CSI. Thus, present reaction provides a simple synthetic route to 2-oxazoline and 2-imidazolidinone. These 2-oxazolines are important protective groups[31,32] for carboxylic function in organic synthesis, as they are inert towards Grignard reagents and lithium aluminium hydride. Some of the reactions involving the use of 2-oxazolines as protective group are shown in Scheme III.2.10.

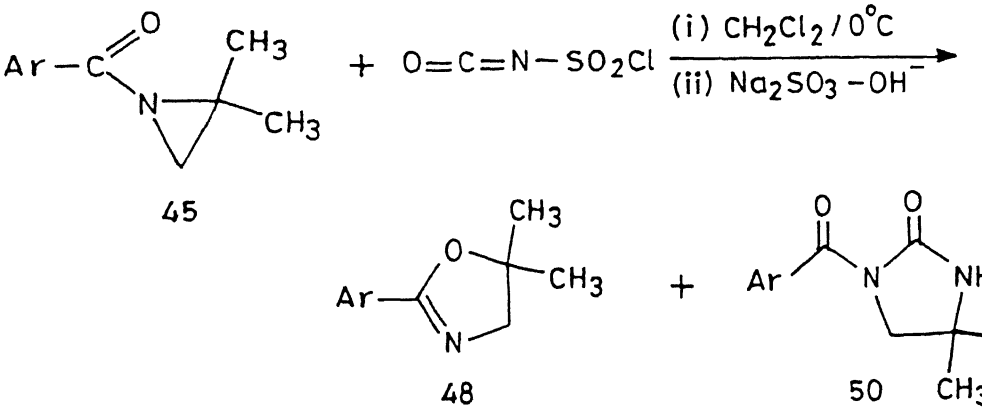
SCHEME III.2.10

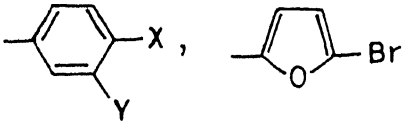


III.3 RESULTS AND DISCUSSION

The reaction of chlorosulfonyl isocyanate with 1-aroyl-aziridines has been studied. The reaction of 1-benzoyl-2,2-dimethyl-aziridine (45a) with CSI at 0°C, followed by hydrolysis, led to the formation of 2-phenyl-5,5-dimethyl-2-oxazoline (48a) and 3-benzoyl--5,5-dimethyl-1,3-imidazolidine-2-one (50a) in 53% and 34% yields respectively (Scheme III.3.1).

SCHEME III.3.1



Ar = 

X = H, CH_3 $C(CH_3)_3$, Br, Cl, OCH_3, NO_2

Y = H, Cl

The structure of the compound **48a** was arrived at on the basis of analytical and spectral data. The elemental analysis and the molecular ion peak at m/z: 175 in its mass spectrum (Fig. III.4) of **48a** indicated that the compound is an isomer of the starting material **45a**. The IR spectrum of **48a**, shown in Fig. III.1, exhibits a strong absorption band at 1640 cm^{-1} indicating the presence of C=N bond. ^{1}H-NMR spectrum of **48a**, shown in Fig. III.2 contains three signals.

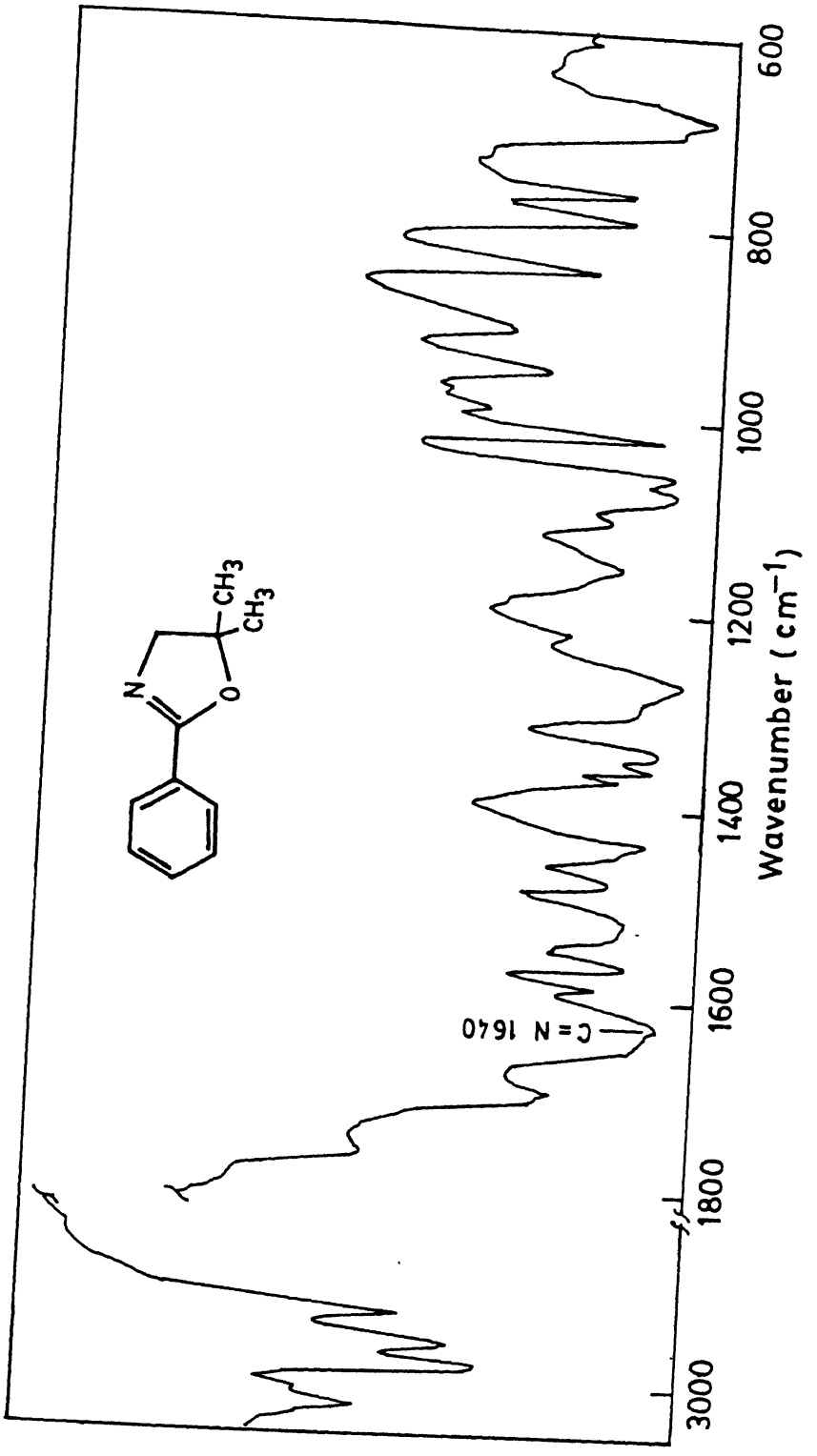


FIG. III.1 I R SPECTRUM OF 48 a

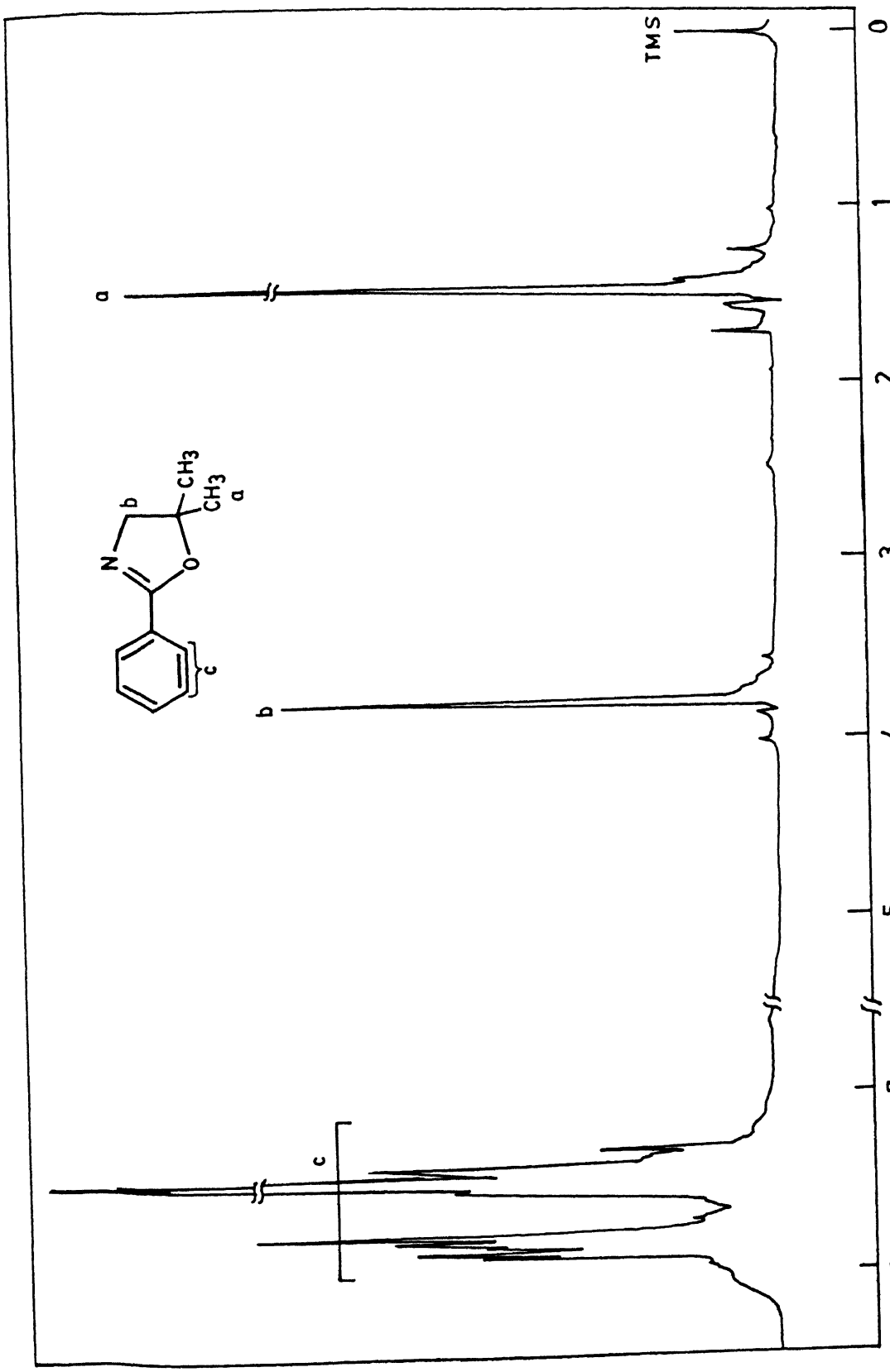


Fig.III.2 ^{1}H-NMR SPECTRUM OF 48 a

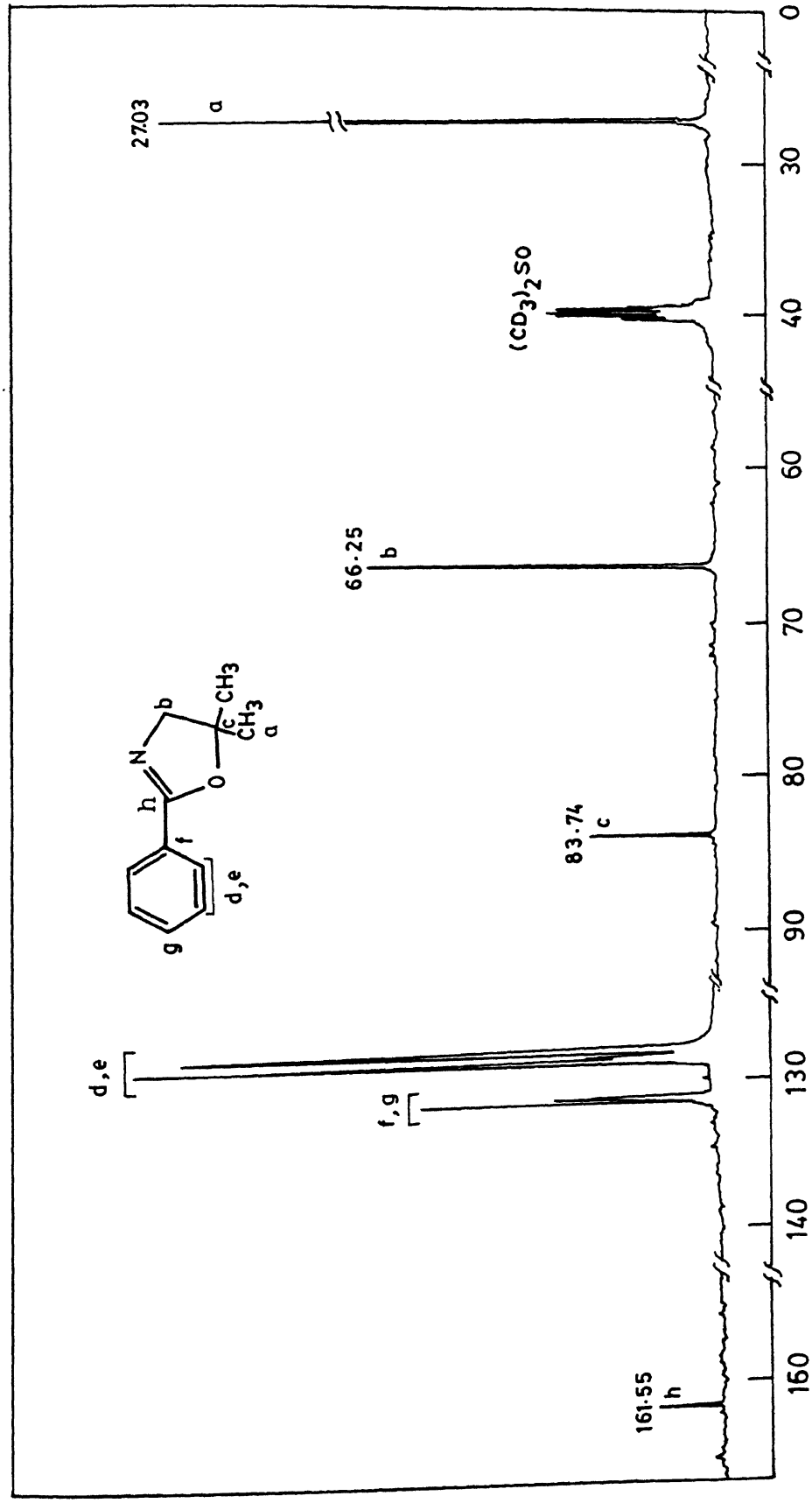


FIG. III.3 ^{13}C-NMR SPECTRUM OF 48a

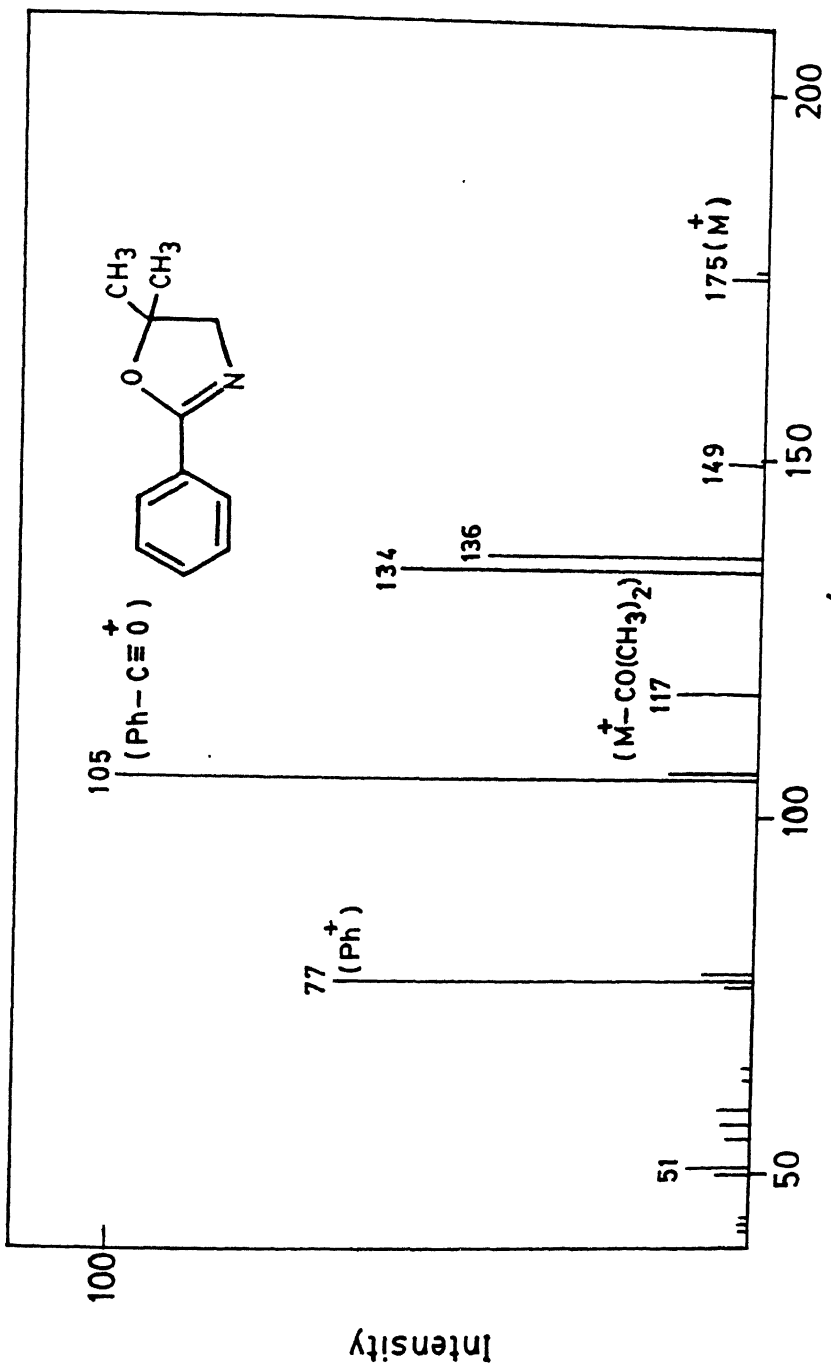


FIG. III.4 MASS SPECTRUM OF 48a

Namely, a singlet at δ 1.42 for *gem*-dimethyl protons, a singlet at δ 3.75 due to methylene protons and a multiplet at δ 7.22-7.95 due to aromatic protons. The ^{1}H-NMR chemical shift values of compound **48a** are in good agreement with the reported values.[32] The structure of compound **48a** is further supported by its ^{13}C-NMR spectrum, shown in Fig. III.3. The ring carbons appeared at δ 66.25 (C_4; =N-CH_2), 83.74 (C_5; -O-$C(CH_3)_2$) and 161.55 (C_2; O-C=N) respectively. These ^{13}C-NMR signals are in good agreement with the assigned structure. Other signals are due to *gem*-dimethyl carbon atom and aromatic carbon atoms. The important fragments in the mass spectrum (Fig. III.4) of **48a** are at m/z: 175 (M^+), 160 ($M^+ - CH_3$), 117 ($M^+ - (CH_3)_2CO$) and 105 (Ph-C≡O^+; base peak). The peak at m/z 117, formed by the loss of an acetone molecule (58 mass units) from the molecular ion, suggests that the oxazoline is 5,5-disubstituted and not 4,4-disubstituted. On the basis of above analytical and spectral data the structure of **48a** was assigned as 5,5-dimethyl-2-phenyl-2-oxazoline.

Compound **50a**, (m.p.: 176°C) was identified as follows: the analytical data of compound **50a** for the molecular formula $C_{12}H_{14}N_2O_2$ and molecular ion at m/z 218 in its mass spectrum (Fig. III.8) suggest the addition of 43 mass units in the molecular weight of starting material **45a**. The characteristic IR absorption bands at 3250, 1730 and 1640 cm^{-1} indicate the presence of amide (NH) and two amide carbonyl functions respectively. This conclusion was further confirmed by the NMR spectral data. The ^{1}H-NMR spectrum of **50a** (Fig III.6) showed a deuterium exchangeable proton as broad singlet at δ 5.56, which indicated the presence of NH group in the molecule. The other ^{1}H-NMR peaks appear at δ 1.36 (*gem*-dimethyl), 3.81 (methylene) and 7.23-7.76 (aromatic) protons.

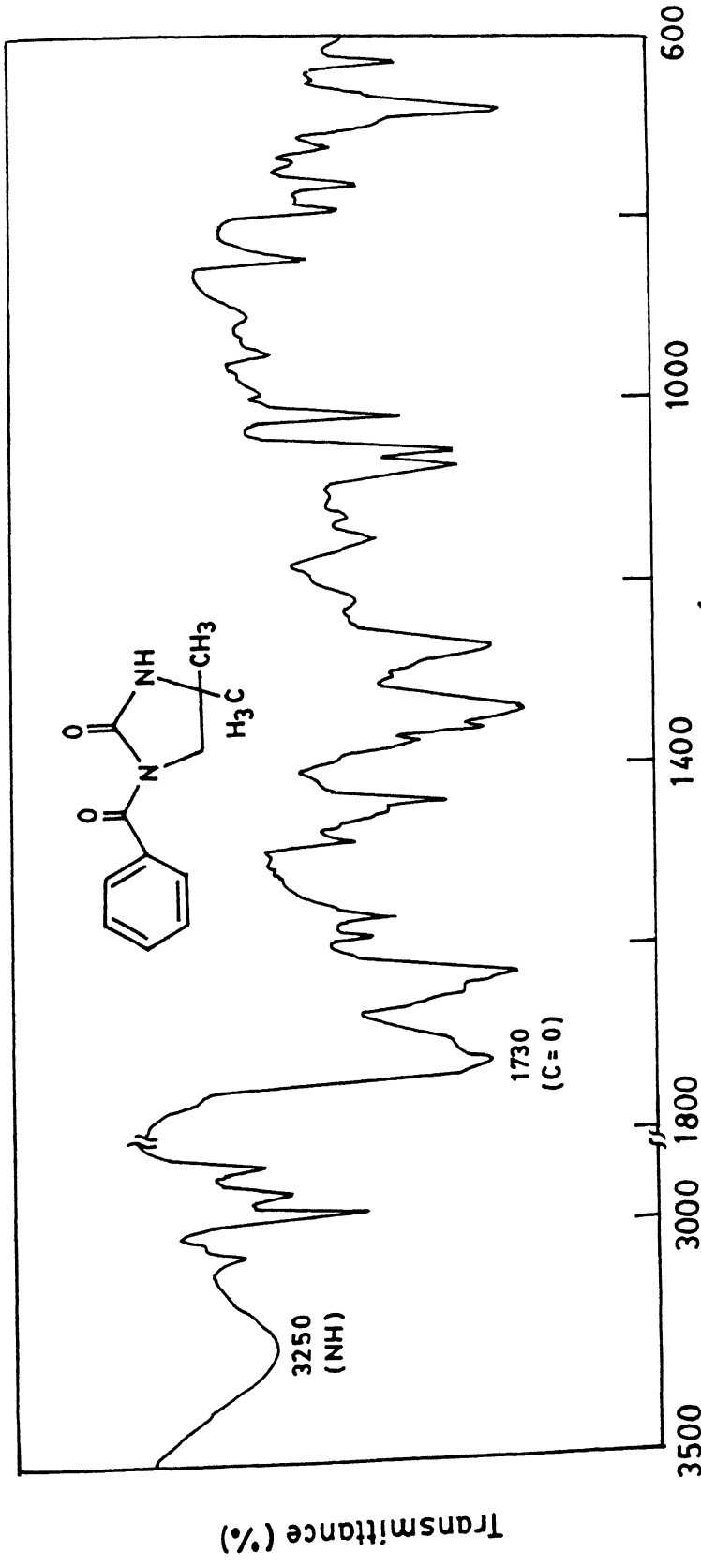


FIG. III.5 I R SPECTRUM OF 50 a

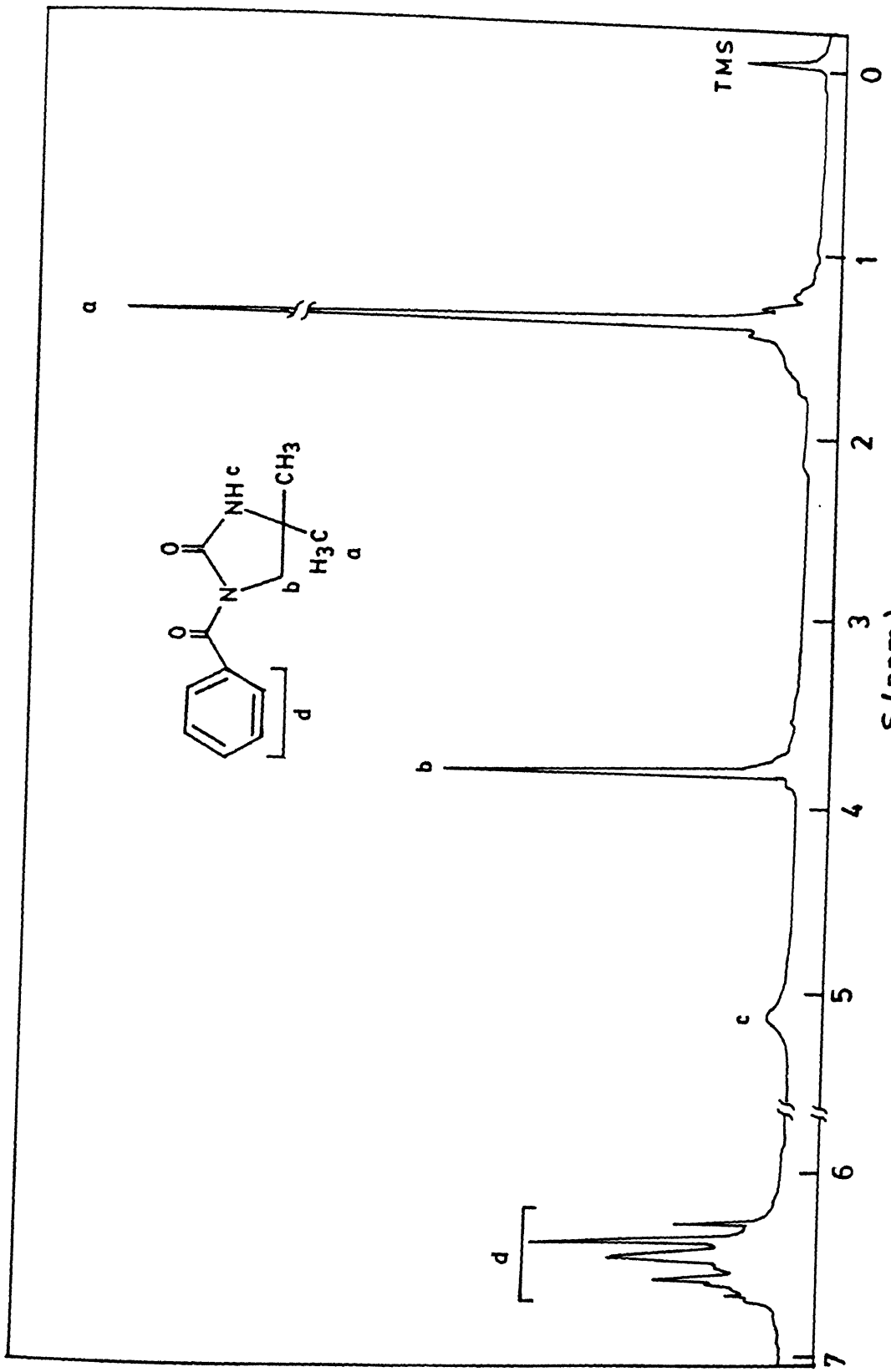


FIG. III. 6 ^{1}H-NMR SPECTRUM OF 50a

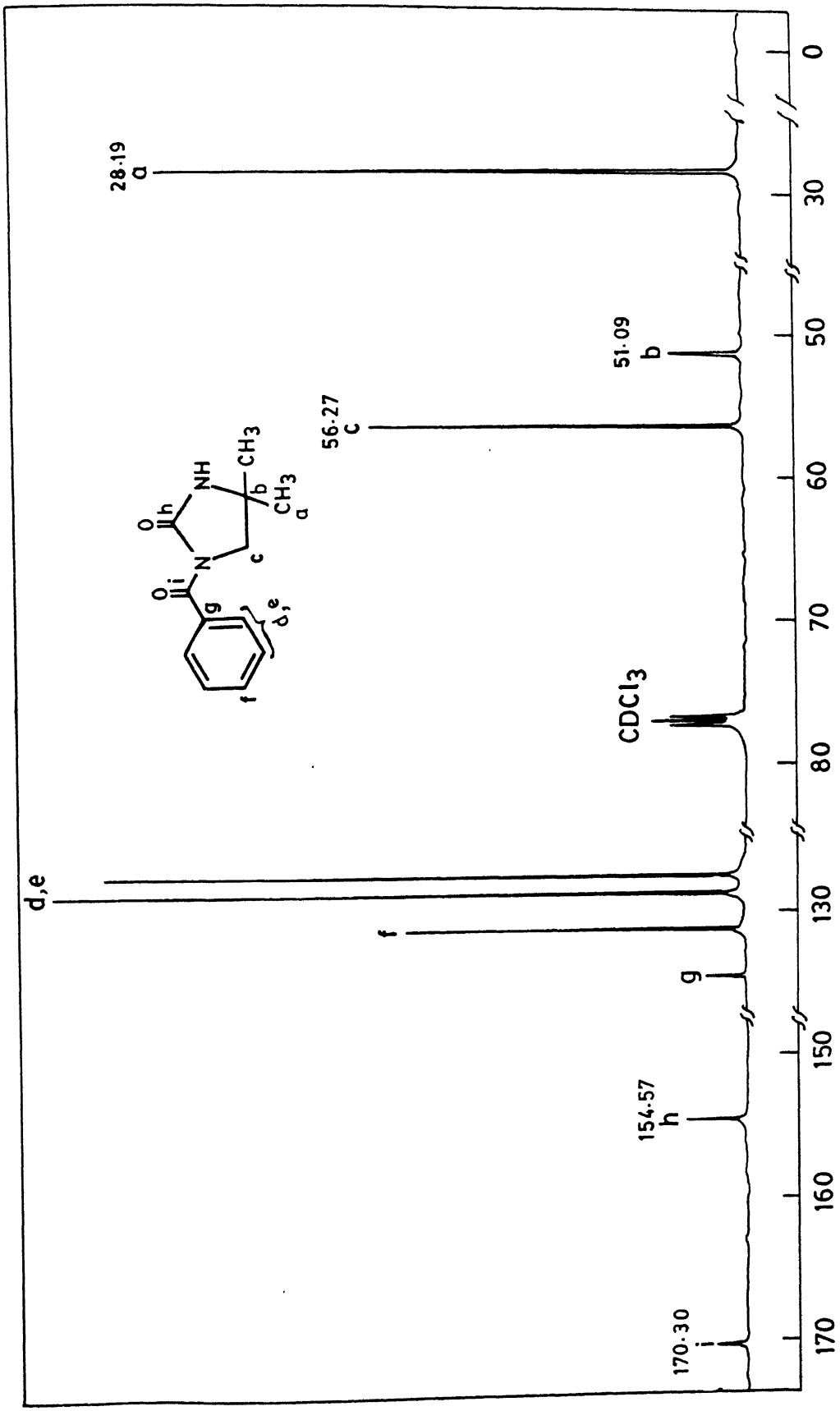


FIG. III. 7 ^{13}C-NMR SPECTRUM OF 50 a

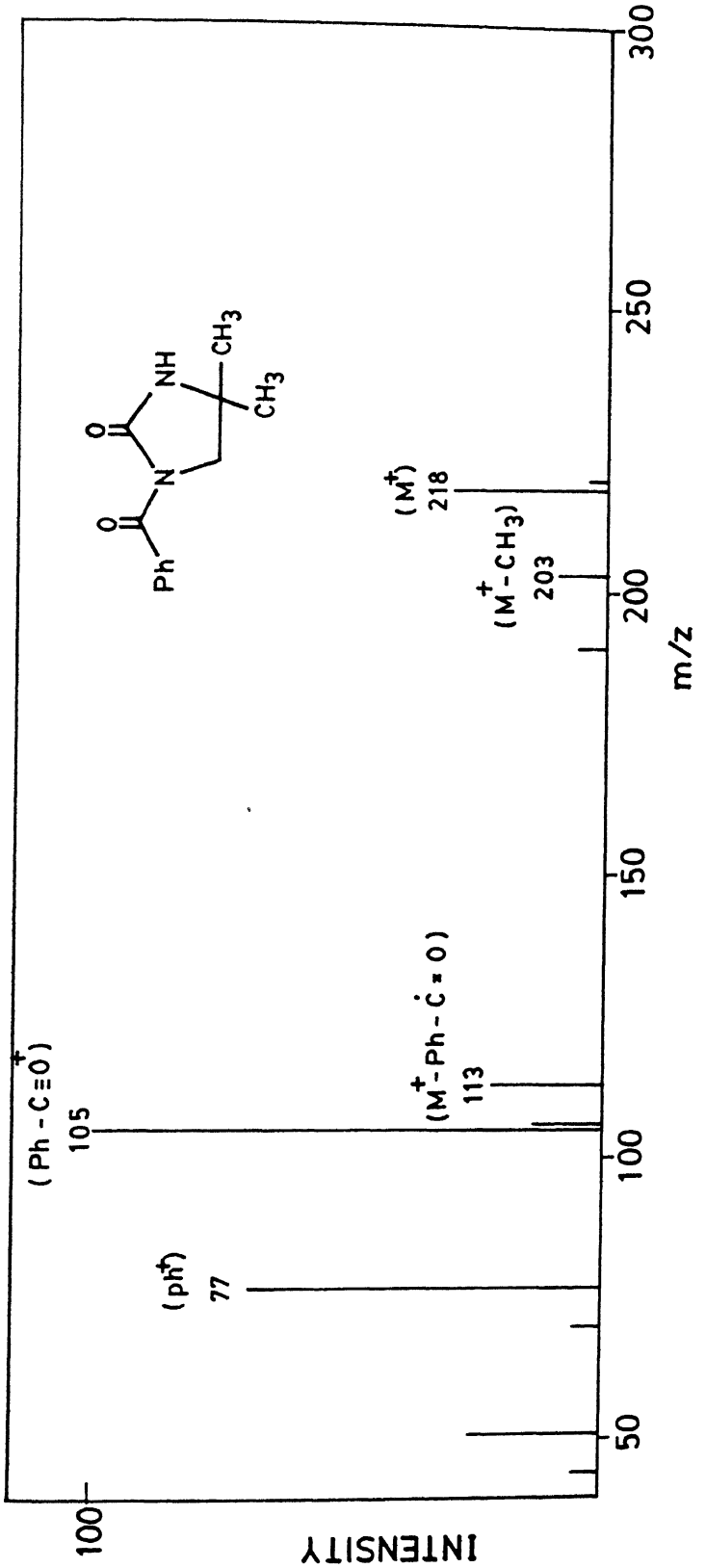


FIG. III-8 MASS SPECTRUM OF 50a

The conclusion was further substantiated by its ^{13}C-NMR spectral data; δ 28.19 (CH_3), 51.09 (C_4; N-CH_2), 56.27 (C_5; $C(CH_3)_2$), 154.57 (C_2; N-CO-NH), 170.32 (Ph-CO-N) as shown in Fig. III.7.

The final proof for the formation of 2-imidazolidinone derivative **50a** has come from the mass spectral data. The fragment peaks are observed at m/z: 218 (M^+), 203 ($M^+ - CH_3$), 190 ($M^+ - CO$), 175 ($M^+ - CONH$), 113 ($M^+ - PhCO^\cdot$) and 105 ($Ph-C\equiv O^+$; base peak) (Fig. III.8). The presence of benzamide carbon signal at δ 170.32 in ^{13}C-NMR spectrum and base peak at m/z: 105 in mass spectrum indicate that the compound **50a** contains a benzoyl group.

Based on the aforesaid analytical and spectral data, the structure of compound **50a** was assigned as 3-benzoyl-5,5-dimethyl--1,3-imidazolidine-2-one.

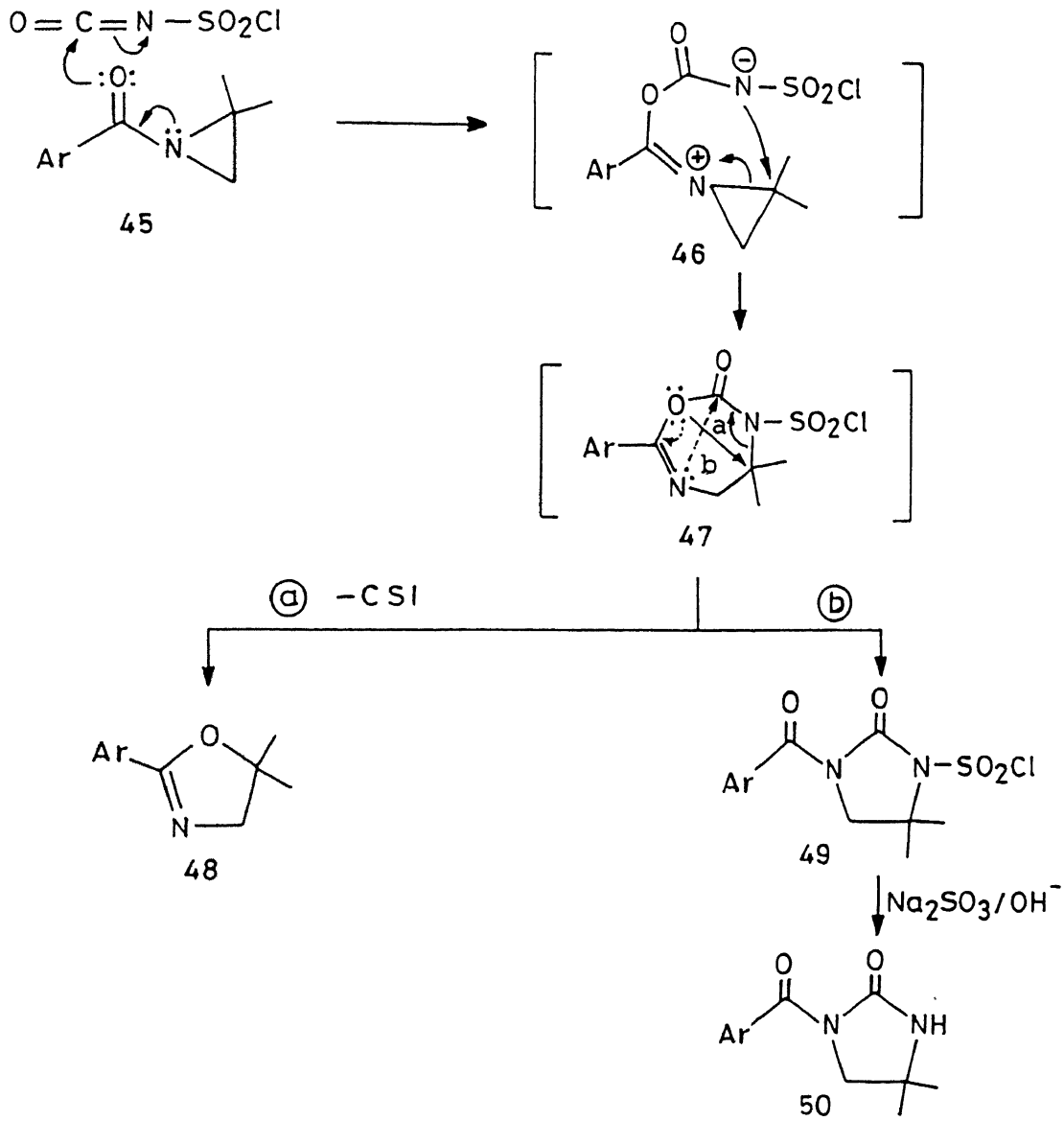
N-Acylaziridines with tetravalent nitrogen possess a pyramidal conformation and undergo nitrogen inversion.[34] Ring opening of such aziridines will generally takes place most easily in the transition state (TS) of this inversion, *i.e.*, when the ring strain is maximal. The aziridine ring and acyl function are coplanar in the transition state of the molecule.[35] The activation energy of the TS is lowered by conjugative stabilization. Applying the above reasoning to the reaction of **45(a-i)** with CSI, a plausible mechanism for the formation of **48(a-i)** and **50(a-h)** is depicted in Scheme III.3.2. The lone pair of carbonyl oxygen atom of **45** attacks the isocyanate group of CSI forming a 1,5-dipolar intermediate *viz.*, aziridinium ion **46**. The aziridinium ion, thus produced, is highly unstable and is, therefore, susceptible to cleavage of N-C_2 bond at the transition state by the attack of the nucleophilic part of the aziridinium ion. This intramolecular cyclization of **46** results in the formation of a seven

membered intermediate **47**. However, due to inherent instability of **47**, it undergoes ring cleavage according to two pathways as shown in Scheme III.3.2. Path (a) involves the intramolecular attack by the lone pair of the oxygen atom (of the ring) on the quaternary carbon atom, followed by extrusion of CSI. This results in the formation of 2-oxazoline derivative **48**. According to path (b) the intermediate **47** rearranges itself by the attack of lone pair of the nitrogen atom on the carbonyl group, leading to a stable five membered 2-imidazolidinone derivative **50** through the intermediacy of **49**. Compound **47** was not isolated, however, its formation during hydrolysis (aqueous sodium sulfite-potassium hydroxide) is predicted, based on the high tendency of $-SO_2Cl$ moiety towards reduction[36] under basic condition.

It is interesting to note that 1-(4-nitrobenzoyl)-2,2-dimethyl-aziridine (**45i**) underwent a smooth reaction with CSI to give only 2-oxazoline derivative **48i** in 76% yield. The strong electron with-drawing effect of $-NO_2$ group reduces the electron density around the nitrogen atom of **47i**. Therefore, intramolecular attack of nitrogen lone pair on the carbonyl group does not favour the formation of **49i** but eliminates a molecule of CSI, resulting in the formation of **48i** (Scheme III.3.2). The structure of 2-(4-nitro-phenyl)-5,5-dimethyl-2-oxazoline (**48i**) was assigned on the basis of its analytical and spectral data and compared satisfactorily with the data obtained from an authentic sample.

In conclusion it may be pointed out here that the present reaction of 1-aroylaziridine with CSI provides a simple synthetic route to 2-oxazoline and 2-imidazolidinone derivatives.

SCHEME III.3.2



III.4 EXPERIMENTAL

Refer to section II.4 for experimental details about the instruments used in this investigation.

III.4.1 Starting materials

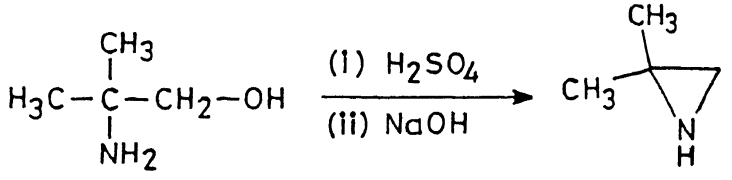
Chlorosulfonyl isocyanate was obtained from Fluka A.G. (Switzerland). 1-Aroylaziridines **45**(a-i) were prepared by the condensation of corresponding aroyl chlorides[16,27] and 2,2-dimethyl-

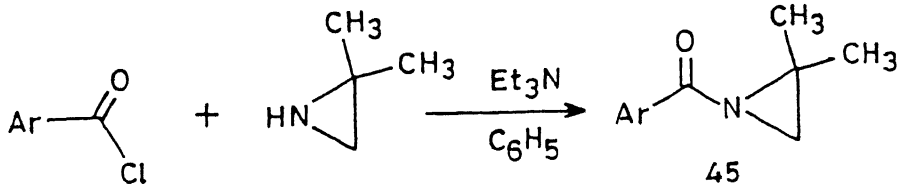
aziridine[28] in the presence triethylamine. Commercial grade solvents were distilled prior to use. Dichloromethane, distilled from P_2O_5 was stored over molecular sieve $4A^0$. Petroleum ether of ($40-60^0C$) grade was used in all the experiments.

III.4.2 Preparation of 1-Benzoyl-2,2-dimethylaziridine (45a)

A solution of benzoyl chloride 2.81 g (20 mmol) in benzene (50 ml) was added dropwise to a mixture of triethylamine 2.02 g (20 mmol) and 2,2-dimethylaziridine 1.42 g (20 mmol) in benzene (100 ml), cooled to 0^0C. The reaction mixture was stirred overnight at room temperature. The salt, triethylamine hydrochloride was separated by filtration. The filtrate was concentrated in *vacuo* to furnish the crude product **45a**, which was purified by column chromatography on neutral alumina using ethyl acetate-petroleum ether (20:80) as eluent. The titled product **45a** separated as a colorless oil. Yield: 2.91 g (83%).

SCHEME III.4.1





III.4.3 Reaction of 1-Benzoyl-2,2-dimethylaziridine (45a) with CSI (General Method)

In a 50-ml Erlenmeyer flask equipped with a magnetic stirring bar and a dropping funnel, was placed **45a** (0.875 g, 5 mmol) and dry dichloromethane (20 ml). The flask was immersed in an ice-bath. A solution of CSI (0.45 ml, 4 mmol) in the same solvent (5 ml) was added slowly for 10 min to the above cooled solution. Stirring was continued for 1h at this temperature and then 2h at ambient temperature to complete the reaction. The reaction mixture was concentrated under reduced pressure to obtained a colorless semi-solid. This semi-solid was dissolved in ether (25 ml) and was slowly added to a stirred mixture of aqueous sodium sulfite (25%, 20 ml) and ether (15 ml) at 5-10^{0}C. The aqueous phase was kept slightly basic by addition of aq.KOH (10%) solution. At the end of reaction (~30 min) the organic layer was separated. Aqueous layer was further extracted with ether (2x20 ml). The combined ethereal extract was washed with water and dried over $MgSO_4$. The solution was concentrated in *vacuo* and residue was subjected to column chromatography over neutral alumina, using ethyl acetate - petroleum ether (1:4; 1:2) as eluent, to furnish **48a** as (Yield: 0.46 g, 53%; colorless oil; Lit. m.p.: 37^{0}C) and **50a** as solid (Yield: 0.37 g, 34%; m.p.: 176^{0}C). Compound **50a** was crystallized from ethyl alcohol in colorless crystals. Analytical and spectral data of products **48a** and **50a** are given below.

Analytical and spectral data of 5,5-dimethyl-2-phenyl-2-oxazoline (48a)

Anal. for $C_{11}H_{13}NO$: Calcd: C, 75.40; H, 7.48; N, 7.99 %

Found: C, 75.31; H, 7.66; N, 8.26 %

IR (thin film) ν_{max} : 1640, 1590, 1390, 1365, 760, 695 $cm.^{-1}$

Mass m/z (rel. int.) : 176 (M^++1, 3), 175 (M^+, 37), 160 (7), 118 (4), 117 (15), 105 (100), 77 (62).

^{1}H-NMR ($CDCl_3$) δ : 1.42 (s, 6H), 3.75 (s, 2H), 7.22-7.95 (m, 5H).

^{13}C-NMR (DMSO-d_6) δ : 27.03, 66.25, 83.74, 127.62, 128.43, 129.33, 131.16, 161.55.

Analytical and spectral data of 3-benzoyl-5,5-dimethyl-1,3-imidazol--idine-2-one (50a)

Anal. for $C_{12}H_{14}N_2O_2$: Calcd: C, 66.03; H, 6.47; N, 12.84 %

Found: C, 65.82; H, 6.58; N, 12.96 %

IR (KBr) ν_{max} : 3250, 1730, 1640, 1430, 1340, 765, 690 $cm.^{-1}$

Mass m/z (rel. int.) : 218 (M^+, 33), 217 (2), 203 (14), 190 (10), 175 (6), 113 (25), 105 (100).

^{1}H-NMR ($CDCl_3$) δ : 1.36 (s, 6H), 3.81 (s, 2H), 5.56 (brs, 1H), 7.23-7.76 (m, 5H).

^{13}C-NMR ($CDCl_3$) δ : 28.19, 51.09, 56.27, 127.38, 128.69, 131.22, 134.53, 154.57, 170.32.

III.4.4 Reaction of 1-(4-bromobenzoyl)-2,2-dimethylaziridine (45b) with CSI

The reaction of CSI (0.36 ml, 4 mmol) with **45b** (1.02 g, 4 mmol) was carried out using the procedure described earlier (cf. Section III.4.3). The residue obtained after aqueous work-up was subjected to column chromatography (neutral alumina and ethyl acetate-petroleum ether; 40:60) to give compounds **48b** and **50b**.

Compound **48b** was crystallized from ether - petroleum ether (4:1). Yield: 0.44 g (43%); m.p.: 57°C (Lit.m.p.: 57-59°C) The other compound **50b** was crystallized from ethanol in light yellow crystals. Yield: 0.26 g (22%); m.p.: 180°C.

Similarly, the reaction of compounds **45** (**c-h**) with CSI was carried out as described in Section III.4.4. The yields and melting points of 2-oxazolines **48**(**a-i**) and 2-imidazolidinones **50**(**a-h**) are given in Table III.1.

Analytical and spectral characteristics of products **48**(**b-h**) and **50**(**b-h**) are given below.

Table III.1

YIELDS AND MELTING POINTS OF 2-OXAZOLINES 48 AND 2-IMIDAZOLIDINONES 50

Sl. No.	Substituent Ar	2-Oxazoline Yield (%)	2-Oxazoline m.p.°C (Lit.)	2-Imidazolidinone Yield (%)	2-Imidazolidinone m.p.°C
a	C_6H_5	53	oil (37)	34	176
b	*p*-Br-C_6H_4	43	57 (59-61)	22	180
c	*p*-CH_3-C_6H_4	55	oil	31	170
d	*m*-Cl-C_6H_4	56	oil	33	131
e	*p*-Cl-C_6H_4	46	oil	24	180-181
f	*p*-(*t*-C_4H_9)-C_6H_4	41	oil	25	128
g	*p*-CH_3O-C_6H_4	44	oil	29	159-160
h	5-Br-2-furyl†	53	oil	31	156-157
i	*p*-NO_2-C_6H_4	76	143 (146-147)	--	--

† = C_4H_2BrO-

2-(4-Bromophenyl)-5,5-dimethyl-2-oxazoline (48b)

Anal. for $C_{11}H_{12}BrNO$: Calcd: C, 51.99; H, 4.76; N, 5.51 %
Found: C, 51.87; H, 4.85; N, 5.67 %

IR (KBr) ν_{max} : 1665, 1585, 1380, 1360, 845 $cm.^{-1}$

Mass m/z (rel. int.) : 255 (M^++2, 12), 253 (M^+, 14), 240 (7), 238 (8), 197 (89), 195 (100), 185 (64), 183 (70), 157 (52), 155 (57).

^{1}H-NMR ($CDCl_3$) δ : 1.48 (s, 6H), 3.76 (s, 2H), 7.41 (d, 2H, J=8.0 Hz), 7.62 (d, 2H, J=8.0 Hz).

3-(4-Bromobenzoyl)-5,5-dimethyl-1,3-imidazolidine-2-one (50b)

Anal. for $C_{12}H_{13}BrN_2O_2$: Calcd: C, 48.50; H, 4.41; N, 9.43 %
Found: C, 48.43; H, 4.57; N, 9.50 %

IR (KBr) ν_{max} : 3230, 1750. 1665, 1590, 1395, 1370, 1340, 840 $cm.^{-1}$

Mass m/z (rel. int.) : 298 (M^++2, 21), 296 (M^+, 19), 283 (14), 281 (14), 270 (10), 268 (9), 255 (7), 253 (6), 239 (8), 237 (8), 185 (92), 183 (100), 157 (27), 155 (20), 113 (36).

^{1}H-NMR ($CDCl_3$) δ : 1.38 (s, 6H), 3.74 (s, 2H), 5.24 (brs, 1H), 7.19 (d, 2H, J=8.0 Hz), 7.74 (d, 2H, J=8.0 Hz).

^{13}C-NMR ($CDCl_3$) δ : 28.39, 51.25, 56.27, 126.09, 130.44, 130.75, 133.26, 154.40, 169.33.

5,5-Dimethyl-2-(4-methylphenyl)-2-oxazoline (48c)

Anal. for $C_{12}H_{15}NO$: Calcd: C, 76.15; H, 7.99; N, 7.40 %
Found: C, 76.02; H, 8.17; N, 7.48 %

IR (thin film) ν_{max} : 1640, 1575, 1395, 1370, 845 $cm.^{-1}$

Mass m/z (rel. int.) : 190 (M^++1, 9), 189 (M^+, 80), 174 (6), 132 (41), 131 (100), 119 (75), 91 (64).

^{1}H-NMR ($CDCl_3$) δ : 1.36 (s, 6H), 2.35 (s, 3H), 3.60 (s, 2H), 7.09 (d, 2H, J=8.0 Hz), 7.78 (d, 2H, J=8.0 Hz).

^{13}C-NMR ($CDCl_3$) δ : 21.07, 27.11, 66.19, 83.68, 127.65, 129.13, 129.37, 141.15, 161.59.

5,5-Dimethyl-3-(4-methylbenzoyl)-1,3-imidazolidine-2-one (50c)

Anal. for $C_{13}H_{16}N_2O_2$: Calcd: C, 67.22; H, 6.94; N, 12.06 %
Found: C, 67.19; H, 6.98; N, 12.14 %

IR (KBr) ν_{max} : 3205, 1730, 1665, 1560, 1390, 1370, 1335, 835 $cm.^{-1}$

Mass m/z (rel. int.) : 233 (M^++1, 10), 232 (M^+, 39), 217 (9), 204 (24), 189 (7), 120 (40), 119 (100), 113 (20), 91 (61).

^{1}H-NMR ($CDCl_3$) δ : 1.32 (s, 6H), 2.38 (s, 3H), 3.76 (s, 2H), 5.29 (brs, 1H), 7.13 (d, 2H, J=8.0 Hz), 7.48 (d, 2H, J=8.0 Hz).

^{13}C-NMR ($CDCl_3$) δ : 21.23, 28.23, 51.17, 56.25, 127.56, 129.36, 135.31, 140.57, 154.50, 169.58.

2-(3-Chlorophenyl)-5,5-dimethyl-2-oxazoline (48d)

Anal. for $C_{11}H_{12}ClNO$: Calcd: C,63.01; H,5.77; N,6.68 %
Found: C,62.87; H,5.83; N,6.71 %

IR (thin film) ν_{max} : 1645, 1570, 1385, 1372, 803, 713 $cm.^{-1}$

Mass m/z (rel. int.) : 211 (M^++2, 7), 209 (M^+, 23), 196 (3) 194 (8),

153 (41), 151 (100), 141 (26), 139 (79), 113 (5), 111 (19).

^{1}H-NMR ($CDCl_3$) δ : 1.44 (s, 6H), 3.79 (s, 2H), 7.30-7.95 (m, 4H).

^{13}C-NMR ($CDCl_3$) δ : 27.35, 66.85, 84.55, 126.13, 128.15, 129.53, 130.07, 131.10, 134.28, 162.05.

3-(3-Chlorolbenzoyl)-5,5-dimethyl-1,3-imidazolidine-2-one (50d):

Anal. for $C_{12}H_{13}ClN_2O_2$: Calcd: C, 57.03; H, 5.18; N, 11.09 %

Found: C, 56.94; H, 5.34; N, 11.15 %

IR (KBr) ν_{max} : 3235, 1746, 1665, 1572, 1390, 1383, 1354, 813, 725 cm.$^{-1}$

Mass m/z (rel. int.) : 254 (M^++2, 12), 252 (M^+, 50), 239 (19), 237 (44), 226 (4), 224 (18), 211 (4), 209 (12), 141 (71), 139 (100), 113 (55), 111 (77).

^{1}H-NMR ($CDCl_3$) δ : 1.36 (s, 6H), 3.79 (s, 2H), 5.33 (brs, 1H), 7.17-7.62 (m, 4H).

^{13}C-NMR ($CDCl_3$) δ : 28.30, 51.27, 56.15, 126.82, 128.76, 131.30, 133.42, 136.18, 154.38, 168.83.

2-(4-Chlorophenyl)-5,5-dimethyl-2-oxazoline (48e)

Anal. for $C_{11}H_{12}ClNO$: Calcd: C, 63.01; H, 5.77; N, 6.68 %

Found: C, 63.09; H, 5.89; N, 6.63 %

IR (thin film) ν_{max} : 1650, 1605, 1390, 1360, 840 cm.$^{-1}$

Mass m/z (rel. int.) : 211 (M^++2, 13), 209 (M^+, 39), 196 (3), 194 (6), 153 (37), 151 (100), 141 (31), 139 (83), 113 (11), 111 (29).

^{1}H-NMR ($CDCl_3$) δ : 1.39 (s, 6H), 3.81 (s, 2H), 7.37 (d, 2H, J=8.0 Hz), 7.82 (d, 2H, J=8.0 Hz).

3-(4-Chlorolbenzoyl)-5,5-dimethyl-1,3-imidazolidine-2-one (50e)

Anal. for $C_{12}H_{13}ClN_2O_2$: Calcd: C, 57.03; H, 5.18; N, 11.09 %

Found: C, 57.11; H, 5.32; N, 10.98 %

IR (KBr) ν_{max} : 3315, 1741, 1642, 1392, 1350, 840 $cm.^{-1}$

Mass m/z (rel. int.) : 254 (M^++2, 7), 252 (M^+, 26), 239 (12), 237 (19), 224 (13), 211 (3), 209 (10), 141 (43), 139 (100), 113 (27), 111 (38).

^{1}H-NMR ($CDCl_3$) δ : 1.36 (s, 6H), 3.75 (s, 2H), 5.57 (brs, 1H), 7.30 (d, 2H, J=8.0 Hz), 7.57 (d, 2H, J=8.0 Hz).

^{13}C-NMR ($CDCl_3$) δ : 28.03, 51.08, 56.14, 127.58, 130.21, 132.80, 137.28, 154.41, 169.11.

2-(4-*tert*-butylphenyl)-5,5-dimethyl-2-oxazoline (48f)

Anal. for $C_{15}H_{21}NO$: Calcd: C, 77.88; H, 9.15; N, 6.06 %

Found: C, 77.92; H, 9.38; N, 5.88 %

IR (thin film) ν_{max} : 1645, 1595, 1385, 1365, 845 $cm.^{-1}$

Mass m/z (rel. int.) : 231 (M^+, 19), 216 (3), 174 (8), 173 (100), 161 (74).

^{1}H-NMR ($CDCl_3$) δ : 1.26 (s, 9H), 1.32 (s, 6H), 3.78 (s, 2H), 6.85 (d, 2H, J=8.0 Hz), 7.82 (d, 2H, J=8.0 Hz).

3-(4-*tert*-butylbenzoyl)-5,5-dimethyl-1,3-imidazolidine-2-one (50f)

Anal. for $C_{16}H_{22}N_2O_2$: Calcd: C, 70.04; H, 8.08; N, 10.21 %

Found: C, 69.92; H, 8.11; N, 10.32 %

IR (KBr) ν_{max} : 3245, 1730, 1650, 1390, 1360, 1330, 840 $cm.^{-1}$

Mass m/z (rel. int.) : 275 (M^++1, 6), 274 (M^+, 35), 259 (81), 246

2-[2-(5-Bromofuryl)]-5,5-dimethyl-2-oxazoline (48h)

Anal. for $C_9H_{10}BrNO_2$: Calcd: C, 44.28; H, 4.13; N, 5.73 %

Found: C, 44.17; H, 4.25; N, 5.80 %

IR (thin film) ν_{max} : 1667, 1561, 1483, 1373, 798 $cm.^{-1}$

Mass m/z (rel. int.) : 245 (M^++2, 19), 243 (M^+, 21), 230 (12), 228 (11), 187 (76), 185 (73), 175 (62), 173 (67), 164 (100), 119 (23), 117 (26).

^{1}H-NMR ($CDCl_3$) δ : 1.47 (s, 6H), 3.77 (s, 2H), 6.43 (d, 1H, J=3.5 Hz), 6.90 (d, 1H, J=3.5 Hz).

3-[2-(5-Bromofuroyl)]-5,5-dimethyl-1,3-imidazolidine-2-one (50h)

Anal. for $C_{10}H_{11}BrN_2O_3$: Calcd: C, 41.83; H, 3.86; N, 9.76 %

Found: C, 41.78; H, 3.97; N, 9.81 %

IR (KBr) ν_{max} : 3236, 1750, 1655, 1391, 1361, 752 $cm.^{-1}$

Mass m/z (rel. int.) : 288 (M^++2, 8), 286 (M^+, 9), 273 (3), 271 (3), 207 (100), 175 (67), 173 (55), 119 (18), 117 (19), 113 (3).

^{1}H-NMR ($CDCl_3$) δ : 1.41 (s, 6H), 3.84 (s, 2H), 5.35 (brs, 1H), 6.45 (d, 1H, J=3.5 Hz), 7.43 (d, 1H , J=3.5 Hz).

III.4.5. Reaction of 1-(4-nitrobenzoyl)-2,2-dimethylaziridine (45i) with CSI

The reaction CSI (0.45 ml, 5 mmol) with aziridine **45i** (1.10 g, 5 mmol), was carried out at 0^0C using the same procedure as described under Section III.4.4. The residue obtained was treated with aq. sodium sulfite-potassium hydroxide solution. It was further extracted with ether (3x20 ml). Organic layer was washed with water, dried

(Na_2SO_4) and concentrated in *vacuo* to give **48i**. Compound **48i** was crystallized with aqueous methanol (70%) as light yellow crystals. Yield: 0.84 g (76%); m.p.: 143°C (Lit. m.p.: 146-147°C).[16] The mixed melting point with an authentic sample remained undepressed.

Analytical and spectral data of 5,5-dimethyl-2-(4-nitrophenyl)-2--oxazoline (48i)

Anal. for $C_{11}H_{12}N_2O_3$: Calcd: C, 59.99; H, 5.49; N, 12.72 %
Found: C, 59.86; H, 5.62; N, 12.89 %

IR (KBr) ν_{max} : 1639, 1597, 1526, 1344, 1280, 1084, 802 $cm.^{-1}$

Mass m/z (rel. int.) : 220 (M^+, 15), 205 (4), 174 (12), 162 (100), 122 (37).

^{1}H-NMR ($CDCl_3$) δ : 1.43 (s, 6H), 3.96 (s, 2H), 7.56 (d, 2H, J=8.5 Hz), 8.20 (d, 2H, J=8.5 Hz).

^{13}C-NMR ($CDCl_3$) δ : 27.26, 67.16, 84.90, 123.44, 129.11, 134.61, 149.01, 161.65.

REFERENCES

1. S. Gabriel, *Chem. Ber.*, 1888, 21, 1049.
2. P.E. Fanta, "*Chemistry of Heterocyclic Compounds*", Ed. Weissberger, Part I, Interscience Publishers, New York, 1964.
3. O.C. Dermer, G.E. Ham, "*Ethyleneimine and other Aziridines*", Academic Press, New York, N.Y., 1969, pp.257-260.
4. F.W. Fowler, *Adv. Heterocycl. Chem.*, 1971, **13**, 45.
5. A.Padwa, A.D. Woolhouse, "*Comprehensive Heterocyclic Chemistry*" Ed. W. Lwowski, Pergamon Press, Oxford, 1984, Vol. 7, p. 47.
6. R. Huisgen, W. Scheer, H. Huber, *J. Am. Chem. Soc.*, 1967, **89**, 1753.
7. R.C. Elderfield, R.S. McElhinney, *J. Org. Chem.*, 1961, **26**, 1917.
8. E. Gulbins, R. Morlock, K. Hamann, *Justus Liebigs Ann. Chem.*, 1966, **698**, 180.
9. J.W. Lown, *Rec. Chem. Progr.*, 1971, **32**, 51; *Chem. Abstr.*, 1972, **76**, 3599g.
10. (a) R. Huisgen, H. Maeder, *J. Am. Chem. Soc.*, 1971, **93**, 1777.
    (b) R. Huisgen, H. Hermann, H. Maeder, *J. Am. Chem. Soc.*, 1971, **93**, 1779.
11. E. Brunn, R. Huisgen, *Tetrahedron Lett.*, 1971, 473.
12. J.W. Lown, G. Dallas, J.P. Moser, *J. Chem. Soc. (C)*, 1970, 2383.
13. H. Nozaki, S. Fujita, R.Noyori, *Tetrahedron*, 1968, **24**, 2193.
14. K.S. Keshavamurthy, D.N. Dhar, *J. Heterocycl. Chem.*, 1984, **21**, 1699.
15. H.W. Heine, Z. Proctor, *J. Org. Chem.*, 1958, 23, 1554.

16. H.W. Heine, M.E. Fetter, E.M. Nicholson, *J. Am. Chem. Soc.*, 1959, **81**, 2202.

17. H.W. Heine, *Angew. Chem. Int. Ed. Engl.*, 1962, **1**, 528.

18. A. Hassner, A. Kascheres, *Tetrahedron Lett.*, 1970, 4623.

19. J. Lehmann, H. Wamhoff, *Synthesis*, 1973, 546.

20. J.F. Dellaria Jr., K.J. Sallin, *Tetrahedron Lett.*, 1990, **31**, 2661.

21. J.E. Dolfini, J.D. Simpson, *J. Am. Chem. Soc.*, 1965, **87**, 4381.

22. H.W. Heine, G.D. Wachob, *J. Org. Chem.*, 1972, **37**, 1049.

23. M.A. Calcagno, H.W. Heine, C. Kruse, W.A. Kofke, *J. Org. Chem.*, 1974, **39**, 162.

24. P.E. Fanta, A.S. Deutsch, *J. Org. Chem.*, 1958, **23**, 72.

25. P.B. Talukdar, P.E. Fanta, *J. Org. Chem.*, 1959, **24**, 526.

26. F. Winternitz, M. Mousseron, R. Dennilauler, *Bull. Soc. Chim. France*, 1956, 382.

27. J. Werry, P. Lin, K. Bellos, P. Assithianakis, H. Stamm, *J. Chem. Soc., Chem. Commun.*, 1990, 1389.

28. H. Stamm, A. Sommer, A. Woderer, W. Wiesert, T. Mall, P. Assithianakis, *J. Org. Chem.*, 1985, **50**, 4946.

29. J. Werry, H. Stamm, P. Lin, R. Falkenstein, S. Gries, H. Irngartinger, *Tetrahedron*, 1989, **45**, 5015.

30. J. Daniel, D. Shukla, D.N. Dhar, *Chem. Lett.*, 1992, 1575.

31. J.A. Frump, *Chem. Rev.*, 1971, **71**, 483.

32. A.I. Meyers, D.L. Temple, D. Haidukewych, E.D. Mihelich, *J. Org. Chem.*, 1974, **39**, 2787.

33. R.M. Silverstein, G.C. Bassler, T.C. Morrill, "*Spectrometric Identification of Organic Compounds*", Fifth Ed., John Wiley & Sons, Inc., 1991, pp. 227-265.

34. (a) H.M. Zacharias, L.M. Trefonas, *J. Heterocycl. Chem.*, 1968, **5**, 343.

(b) E.P. Gopalakrishna, *Acta Crystallogr., Sect.* B, 1972, **B28**, 2754.

35. J.M. Lehn, *Fortschr. Chem. Forsch.*, 1970, **15**, 311; *Chem. Abstr.*, 1971, **74**, 67769d.

36. T. Durst, M.J.O'Sullivan, *J. Org. Chem.*, 1970, **35**, 2043.

37. K.N. Campbell, A.H. Sommers, B.K. Campbell, "*Organic Synthesis*", Collect. Vol. **III**, John Wiley, New York, N.Y., 1955, p. 148.

CHAPTER IV

CYCLIZATION OF 2'-AMINOCHALCONES WITH CHLOROSULFONYL ISOCYANATE

IV.1 ABSTRACT

The use of chlorosulfonyl isocyanate in the synthesis of potential bio-active compounds *viz.*, 2(1H)-quinazolinones and 1H-2,1,3-benzothiadiazine-2,2-dioxide has been studied. It has been found that CSI reacts with 2'-aminochalcone* at low temperature (~-10°C) to yield 4-styryl-2(1H)-quinazolinones **18**(a-g) and 4-styryl-1H-2,1,3-benzothiadiazine-2,2-dioxide **19**(a-f). A plausible mechanism which could account for the formation of both the products has been advanced (*vide infra*, Scheme IV.3.2). It is interesting to note that the 2'-amino-4-nitrochalcone (**17f**) under similar conditions gives only one product *i.e.* 4-(4-nitrostyryl)-2(1H)-quinazolinone (**19f**). The structures of these heterocycles are confirmed on the basis of their analytical and spectral data.

IV.2 INTRODUCTION

The synthesis of novel heterocycles, by the use of CSI and α,β-unsaturated ketones, are well documented in literature.[1,2] The reaction of CSI with 2'-hydroxychalcones[3] is reported to yield the corresponding *o*-carbamoyl-2-hydroxychalcones and benzoxathiazine-2,2--dioxide derivatives (*vide supra*, Section I.1). 2'-Aminochalcones are analogues of 2'-hydroxychalcones and may give novel heterocycles on

---

*IUPAC NAME - 1-(2-aminophenyl)-3-phenyl-2-propen-1-one.

reaction with CSI. This opportunity was exploited to prepare 2-quinazolinone and 2,1,3-benzothiadiazine-2,2-dioxide derivatives by the reaction of 2'-aminochalcones and CSI.

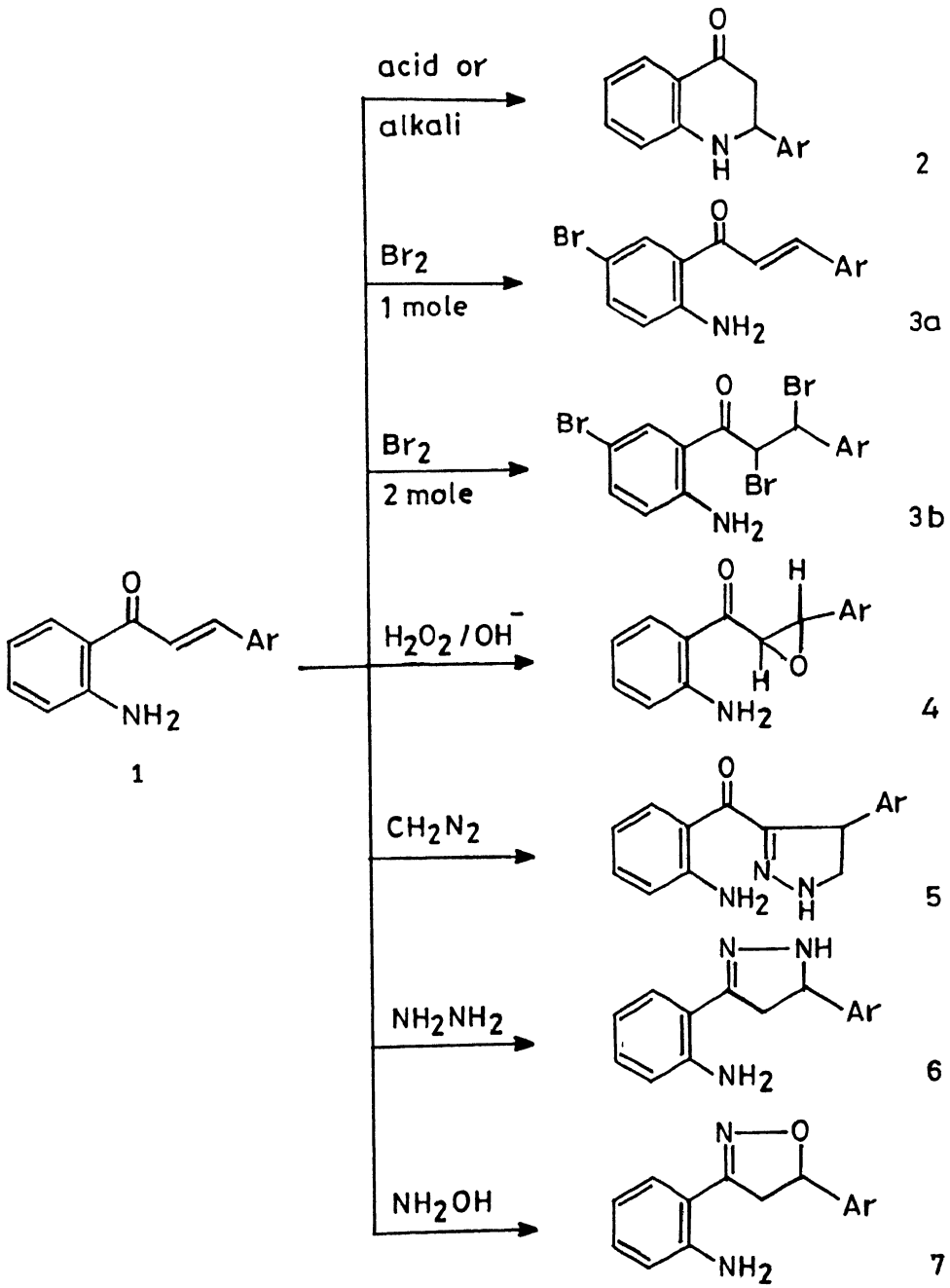
2'-Aminochalcones (**1**) are conveniently prepared by the method of Wattanasin and Murphy.[4] Literature survey indicates that only a small amount of work has been carried out on the chemistry of 2'-aminochalcones. Recent investigations have shown that **1** undergoes several different as well as similar reactions to that of the corresponding oxygen analogue.

Cyclization of 2'-aminochalcone (**1**) with alkali or acid yielded the 2,3-dihydro-2-phenyl-4(1H)-quinolone (**2**). Reaction of **1** with one mole equivalent of bromine gave 2'-amino-5'-bromochalcone (**3a**). However, two mole equivalents of bromine gave 2,3-dibromo-1-(2-amino--5-bromophenyl)-3-phenylpropen-1-one (**3b**). Oxidation of **1** by alkaline hydrogen peroxide gave the stable epoxide **4**. 2'-Aminochalcones undergo cycloaddition with diazomethane to give 3-(2-aminobenzoyl)-4-aryl-2-pyrazolines (**5**). Hydrazine hydrate and hydroxylamine in ethanol, at reflux temperature, gave pyrazoline **6** and isooxazoline **7** derivatives. The various reaction of 2'-aminochalcone[5,6] are shown in Scheme IV.2.1.

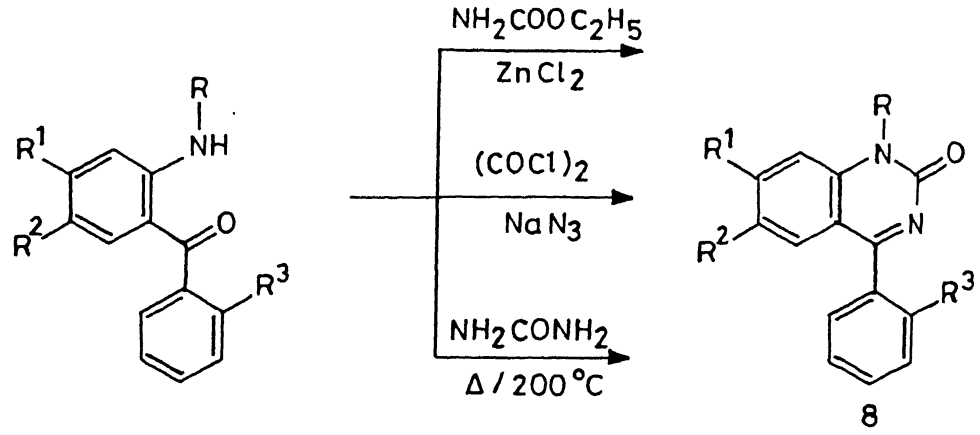
The second part of the introduction illustrates the various synthetic methods available for the preparation of quinazolinones and benzothiadiazine derivatives. 4-Aryl-2(1H)-quinazolinones (**8**) are prepared by the reaction of various reagents such as: (a) ethylcarbamate-$ZnCl_2$, (b) oxalyl chloride-sodium azide[7] and (c) urea[8] and 2'-aminobenzophenones (Scheme IV.2.2).

Under similar reaction conditions *o*-aminoacetophenone yields a charred mass. 4-Methyl-2(1H)-quinazolinones (**9**) are prepared by the

SCHEME IV.2.1

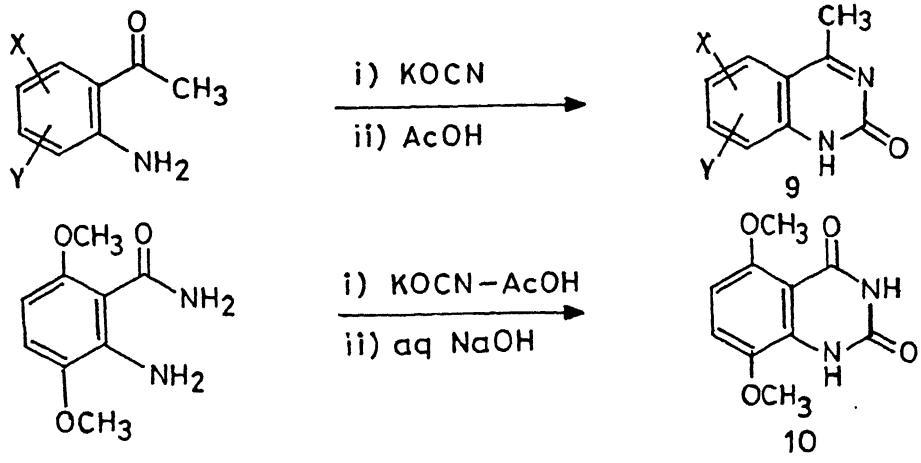

acid or
alkali
2
Br2
1 mole
3a
Br2
2 mole
3b
H2O2 / OH-
4
CH2N2
5
NH2NH2
6
NH2OH
7
1

SCHEME IV.2.2



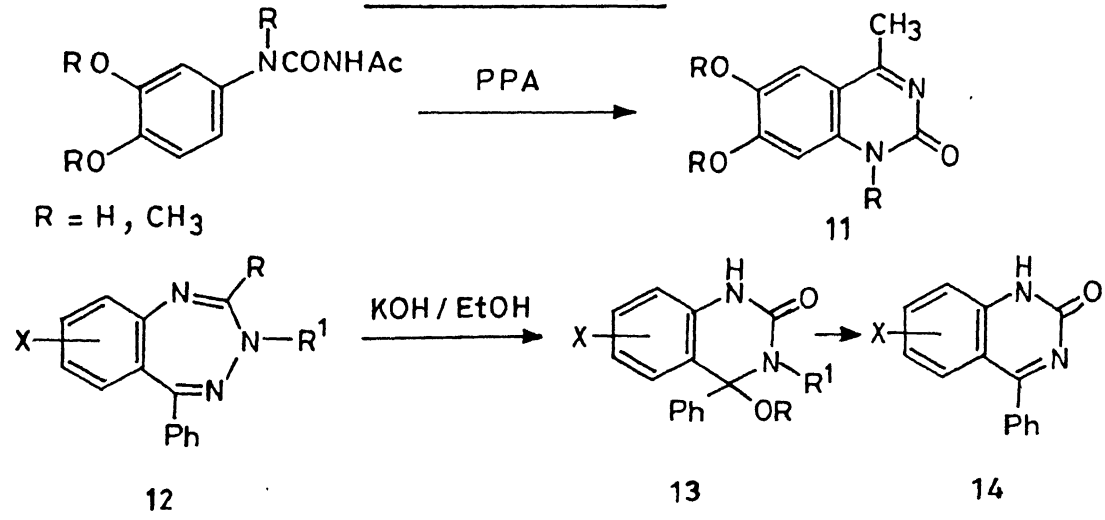
reaction of *o*-aminoacetophenones and potassium cyanate in acetic acid. However, *o*-aminoanthranilamide[9] on reaction with potassium cyanate, followed by hydrolysis with base, gave the corresponding quinazoline-2,4(1H,3H)-dione **10** (Scheme IV.2.3).

SCHEME IV.2.3



N-Acyl-N'-aryl ureas **10**, lacking the ortho substituents in the benzene ring, were cyclized to 4-substituted quinazoline-2(1H)-ones **11** in polyphosphoric acid. Recently Schleuder *et al.*[11], have reported the preparation of 2-quinazolinone by the ring contraction of a seven membered heterocycle. Thus, 5-phenyl-1,3,4-benzotriazepines (**12**) on reaction with ethanolic potassium hydroxide gave 2(1H)-quinazolinones **13** and **14** (Scheme IV.2.4).

SCHEME IV.2.4

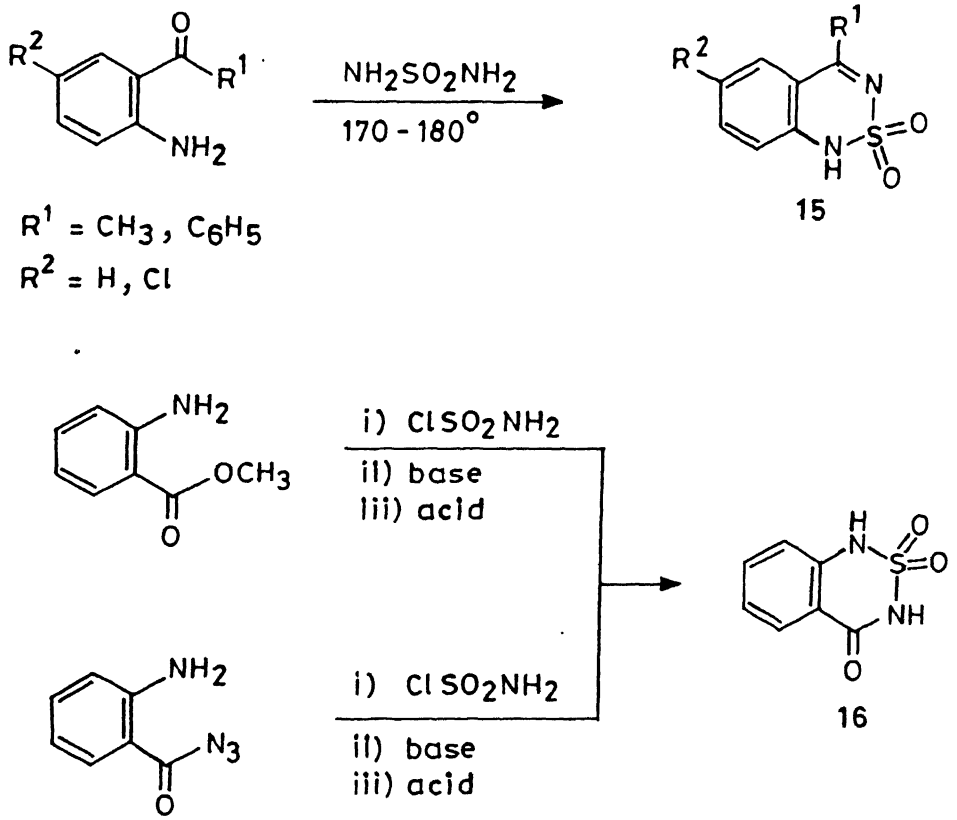


Synthesis of fused thiadiazine systems have been reported by various reagents *e.g.* sulfamide[12] and sulfamoyl chloride.[13] Reaction of 2'-aminoacetophenones or 2'-aminobenzophenones with sulfamide at high temperature afforded 4-substituted 1H-2,1,3-benzothiadiazine--2,2-dioxide **15**. Few synthetic procedures for the preparation of fused thiadiazine systems **15** and **16** are illustrated in Scheme IV.2.5.

Kamal *et al.*[14], have reported the reaction of 2'-aminobenzophenones with CSI (*vide supra*, Section I.1) to give 4-aryl-2(1H)--quinazolinones and 4-aryl-1H-2,1,3-benzothiadiazine-2,2-dioxides.

Herein, we report the preparation of 2(1H)-quinazolinones **18(a-g)** and 1H-2,1,3-benzothiadiazine-2,2-dioxides **19(a-f)** derivatives from the reaction of 2'-aminochalcones and CSI. The heterocycles **18** and **19** contain a substituted vinyl (styryl) group at the fourth position of the ring. This styryl group[15] could be further derivatized and may result in the formation of some interesting compounds.

SCHEME IV.2.5



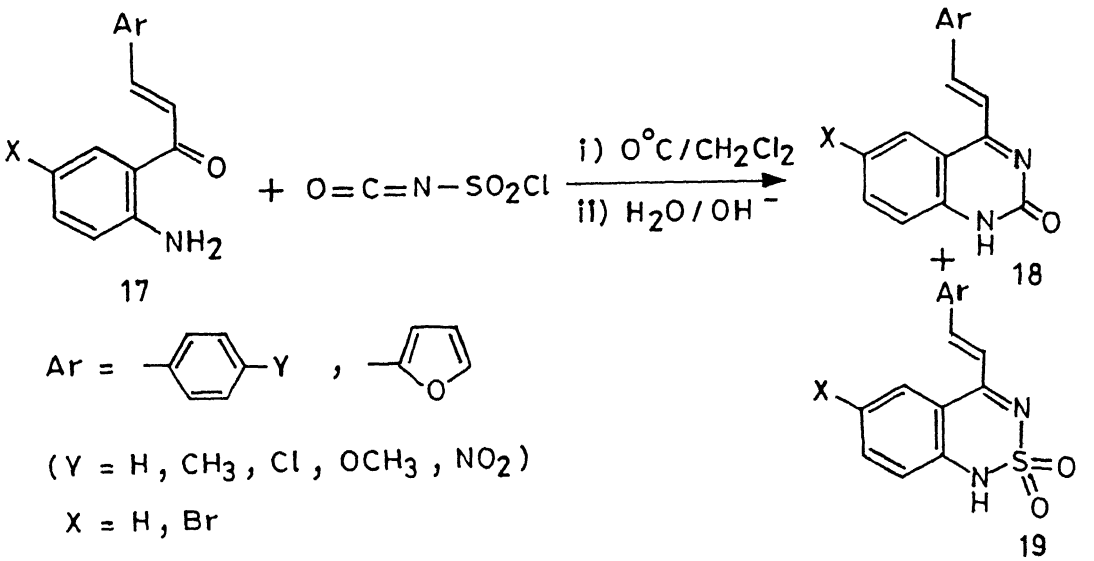
A variety of biological activities has been reported for these heterocycles. The following biological effects have been mentioned for 2(1H)-quinazolinones: antiinflammatory,[16] virucidal,[7] renal vasodilator[10,17] and cardiotonics.[7] Benzothiadiazine dioxides have been claimed to act as sedatives and mild tranquilizers.[18]

IV.3 RESULTS AND DISCUSSION

Reaction of CSI with 2'-aminochalcone (17a) at -10°C gave two products, namely, 2(1H)-quinazolinone 18a and 1H-2,1,3-benzothiadiazine-2,2-dioxide 19a (Scheme IV.3.1). The reaction was carried out in acetonitrile-dichloromethane for 2h at <0°C and ~10h at room

temperature (~25°C). The progress of reaction was monitored by observing the disappearance of the starting material **17a** on tlc. Basic hydrolysis of reaction mixture, followed by neutralization with dil. HCl, gave a yellow precipitate. This on flash column chromatography gave **18a** (43%) and **19a** (16%). The structures of **18a** and **19a** are assigned on the basis of their analytical and spectral characteristics.

SCHEME IV.3.1



The compound **18a** was identified as follows: It showed the molecular ion peak at m/z: 248, in its mass spectrum (Fig. IV.4). The other prominent fragment ions are at m/z: 247 (base peak), 219 (M^+- HCO), 205 (M^+- CONH), 171 (M^+- Ph). The IR spectrum (Fig. IV.1) showed the important IR absorption bands at 3430, 1664 and 1607 $cm.^{-1}$ and indicated the presence of -NH-C(=O)- group in the molecule. The absorption of carbonyl function of **18a** occurs at a lower frequency ($\nu_{C=O}$ 1664 cm^{-1}) than that of 2(1H)-quinazolinone[19] ($\nu_{C=O}$ 1680). This

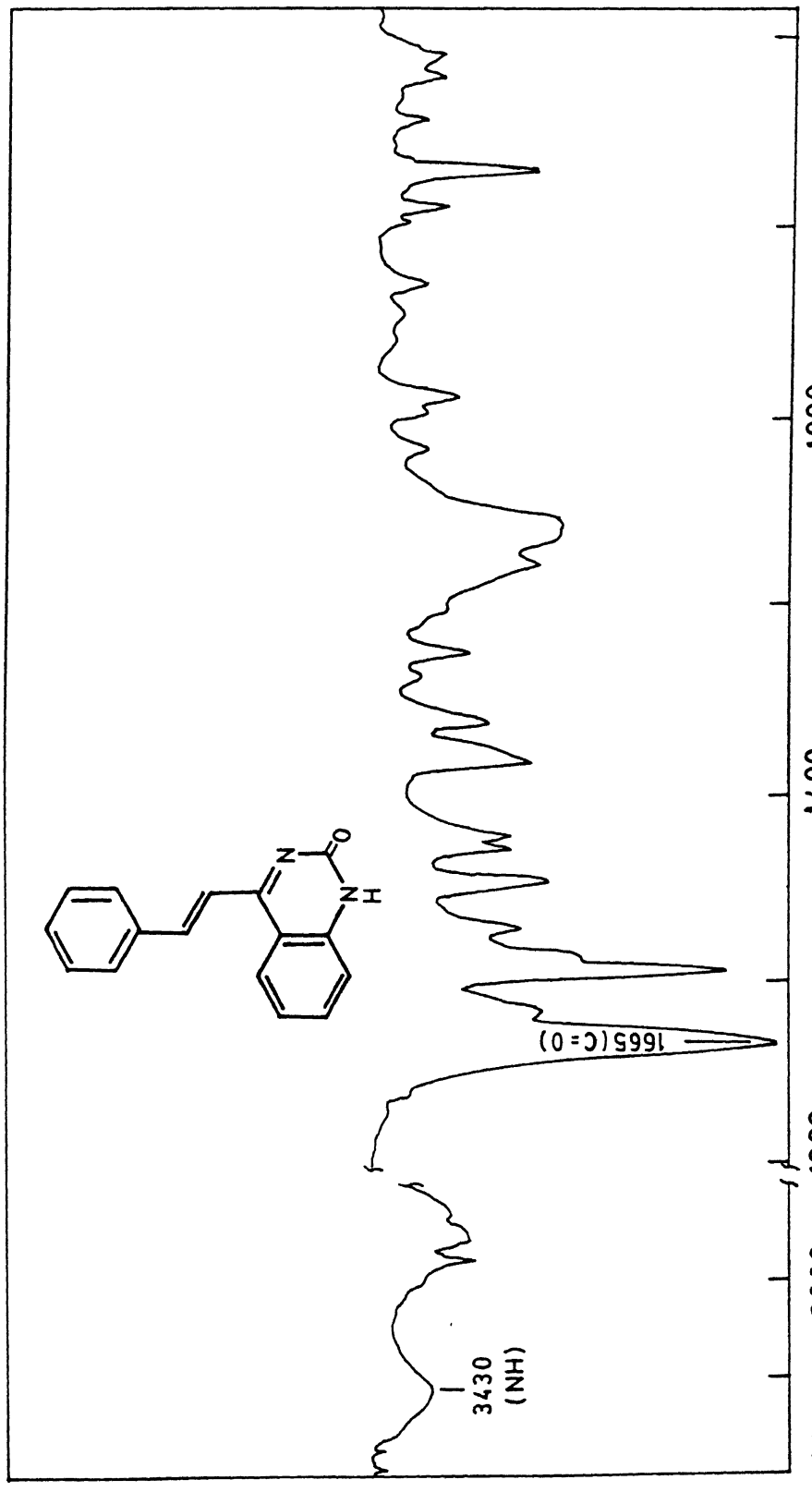


FIG. IV.1 I R SPECTRUM OF 18a

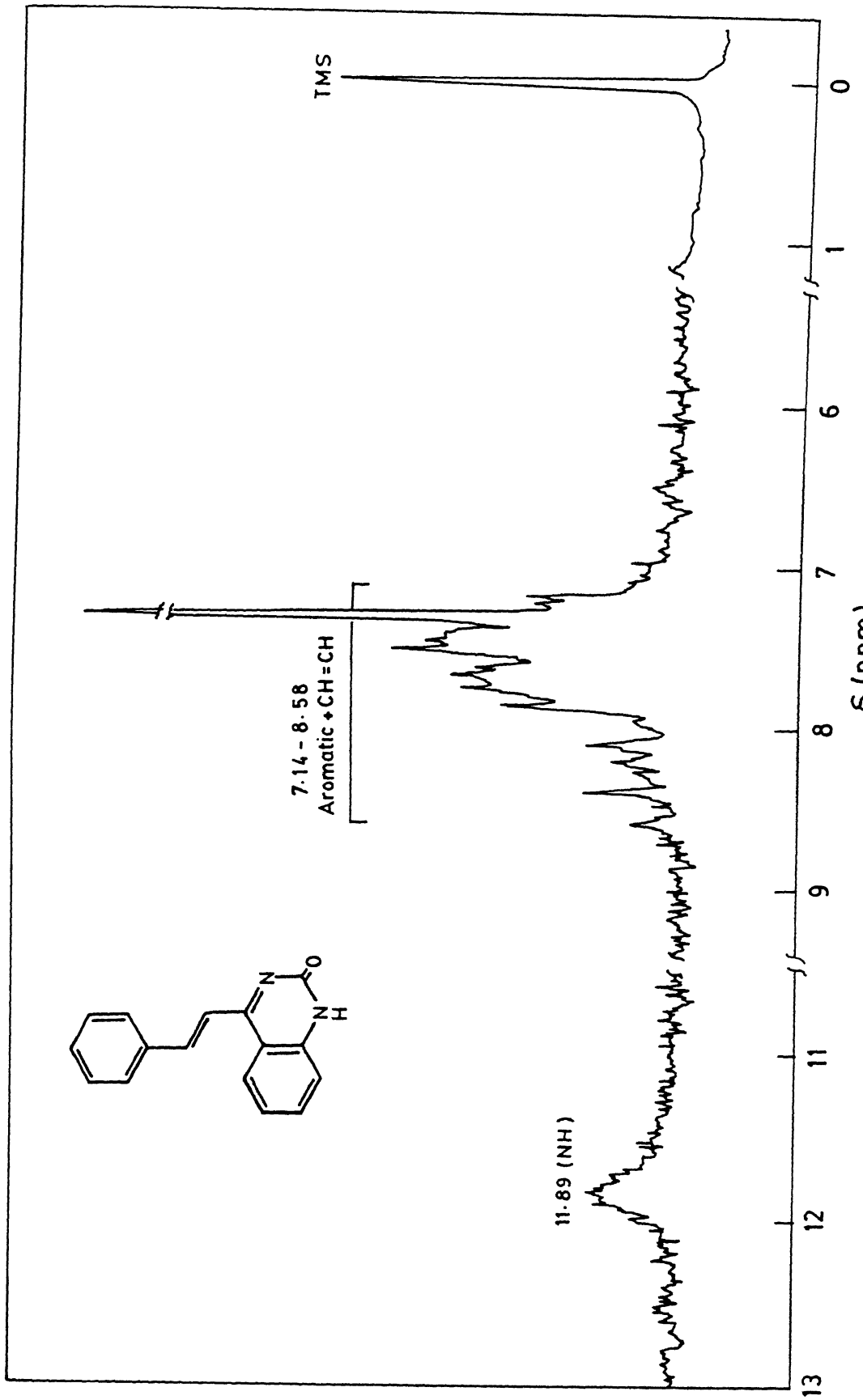


FIG. IV.2 ^{1}H-NMR SPECTRUM OF 18a

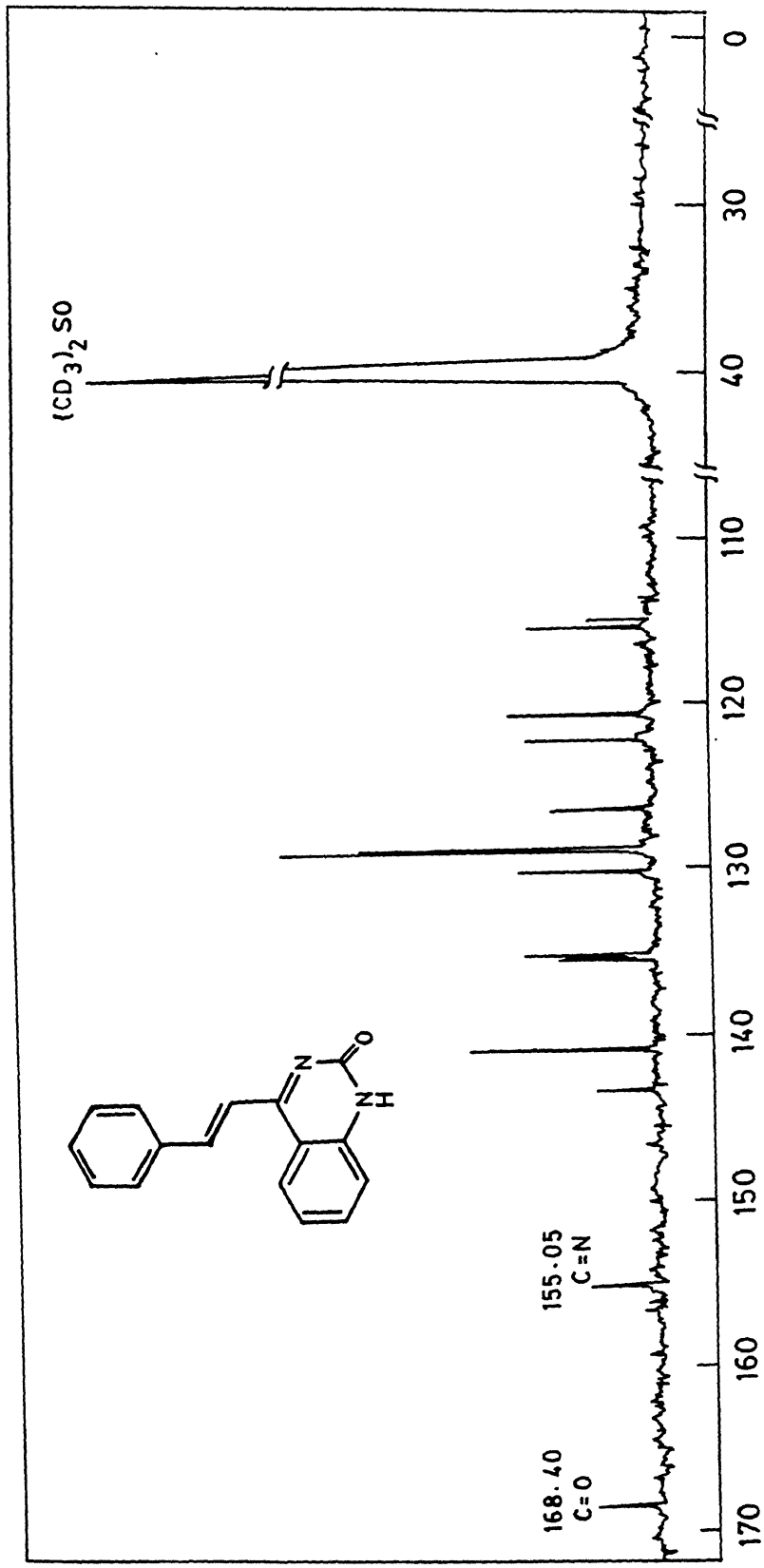


FIG. IV.3 ^{13}C-NMR SPECTRUM OF 18a

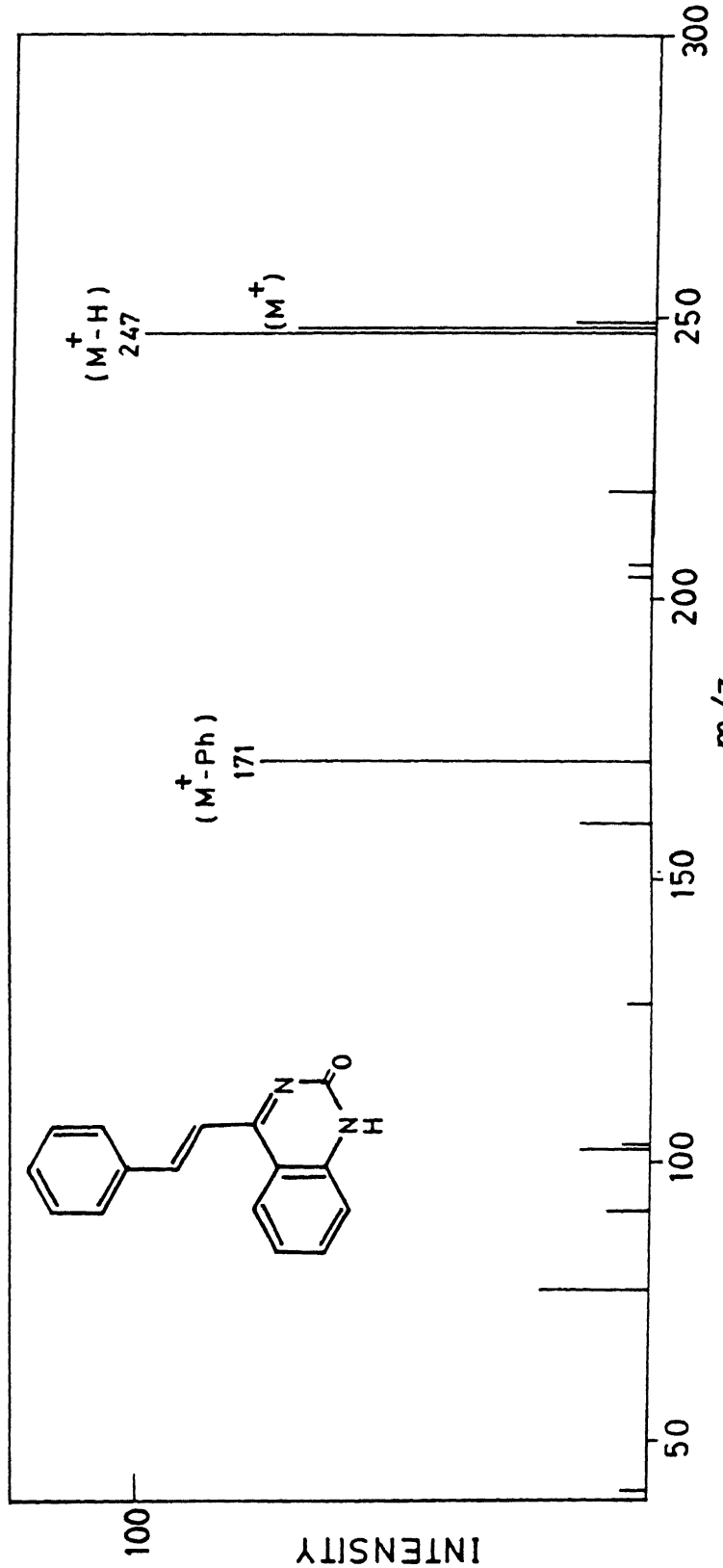


FIG. IV.4 MASS SPECTRUM OF 18a

can be explained in terms of extra conjugation due to the styryl group in the ring. The ^{1}H-NMR spectrum (Fig. IV.2) of the compound **18a** showed a multiplet at δ 7.14-8.58 due to nine aromatic and two olefinic protons. Amide proton (NH) appeared at δ 11.89. It is interesting to note that the amide proton is highly deshielded as compared to normal amides (δ 5.0-8.5). This can be explained in terms of enolic arrangement (-N=C(OH)-) in **18a**. This conclusion was further confirmed by the ^{13}C-NMR spectrum of **18a**, shown in Fig. IV.3. The important signals located at δ 168.40 and 155.04 are due to amide carbon (C_2) and imine carbon (C_4) atoms respectively. The analytical data of **18a** are in good agreement with the molecular formula $C_{16}H_{12}N_2O$.

Based on the aforementioned analytical and spectral data, compound **18a** was assigned as: 4-styryl-2(1H)-quinazolinone.

The structure of 1H-2,1,3-benzothiadiazine-2,2-dioxide derivative **19a** has been elucidated as follows: The compound **19a** exhibited important IR absorption bands at 3210 (NH), 1625 (C=N), 1350 (SO_2, asym.) and 1160 (SO_2, sym.) (Fig. IV.5). The observed IR spectral data were compared with the literature data for 1,2,6-thiadiazine--1,1-dioxide and found to be in good agreement. The ^{1}H-NMR spectrum of **19a** is shown in Fig. IV.6. It showed a multiplet at δ 6.51-7.89 due to aromatic, olefinic and amide protons. It is reported that the sulfonamide proton may appear anywhere in between δ 4-12 and depends on the nature of the solvent and concentration. However, in other similar systems **19(b-f)**, it appeared much downfield (~11 ppm). This conclusion was further supported by the ^{13}C-NMR spectrum of **19a** shown in Fig. IV.7. An important peak at δ 165.63 is assigned to the imine carbon (C_4). Other ^{13}C-NMR signals are due to aromatic and olefinic

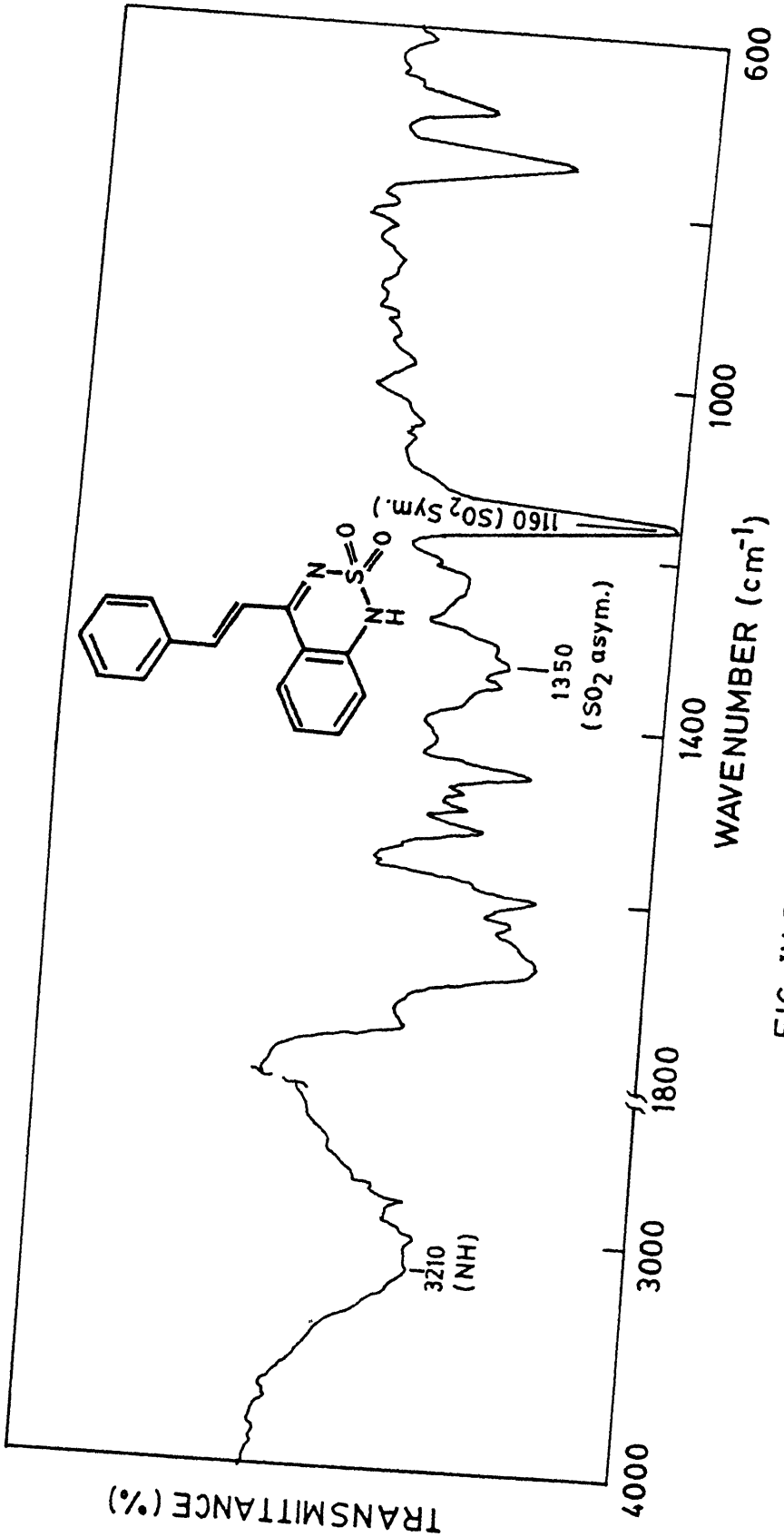


FIG. IV.5 I.R. SPECTRUM OF 19a

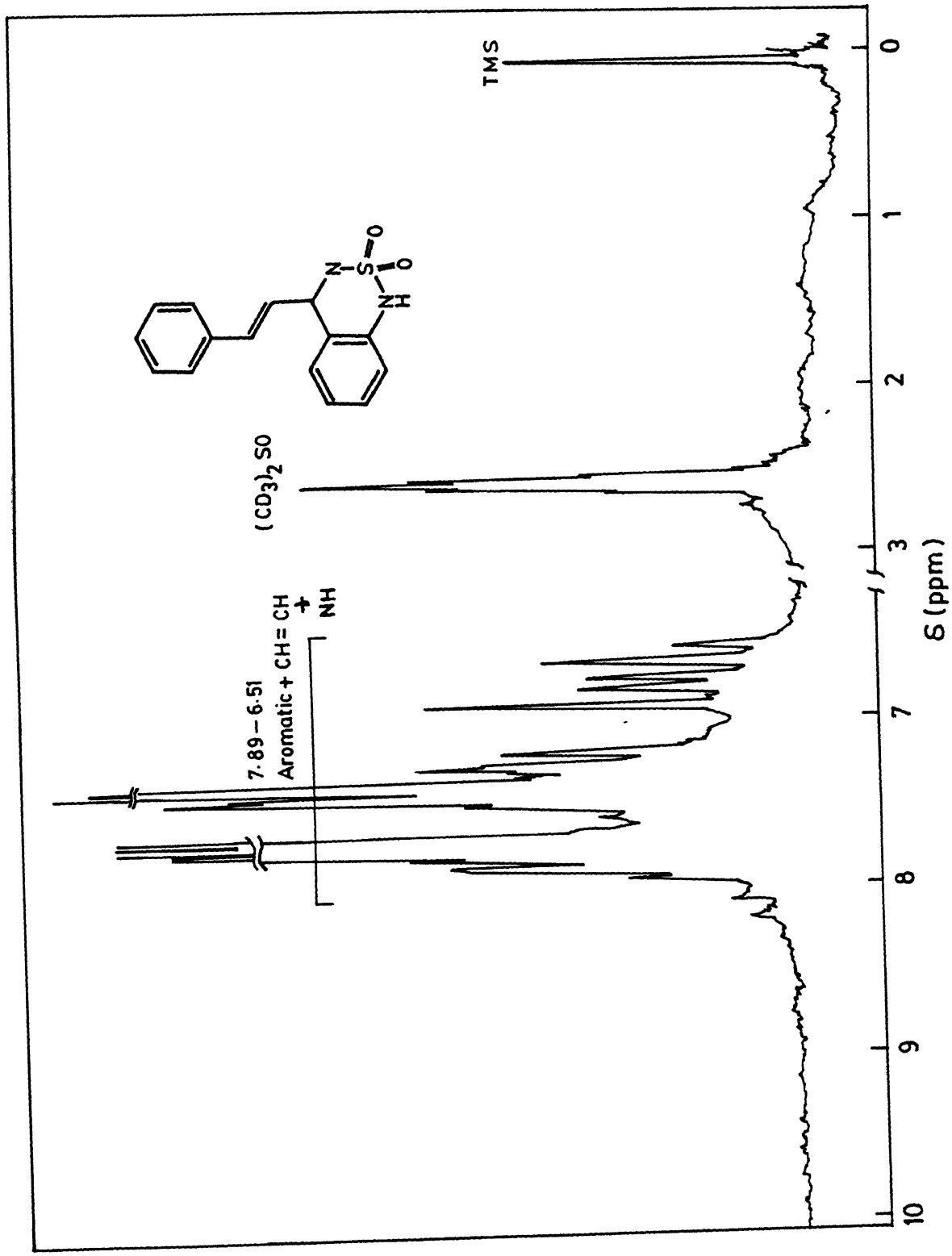


FIG.IV.6 ^{1}H-NMR SPECTRUM OF 19a

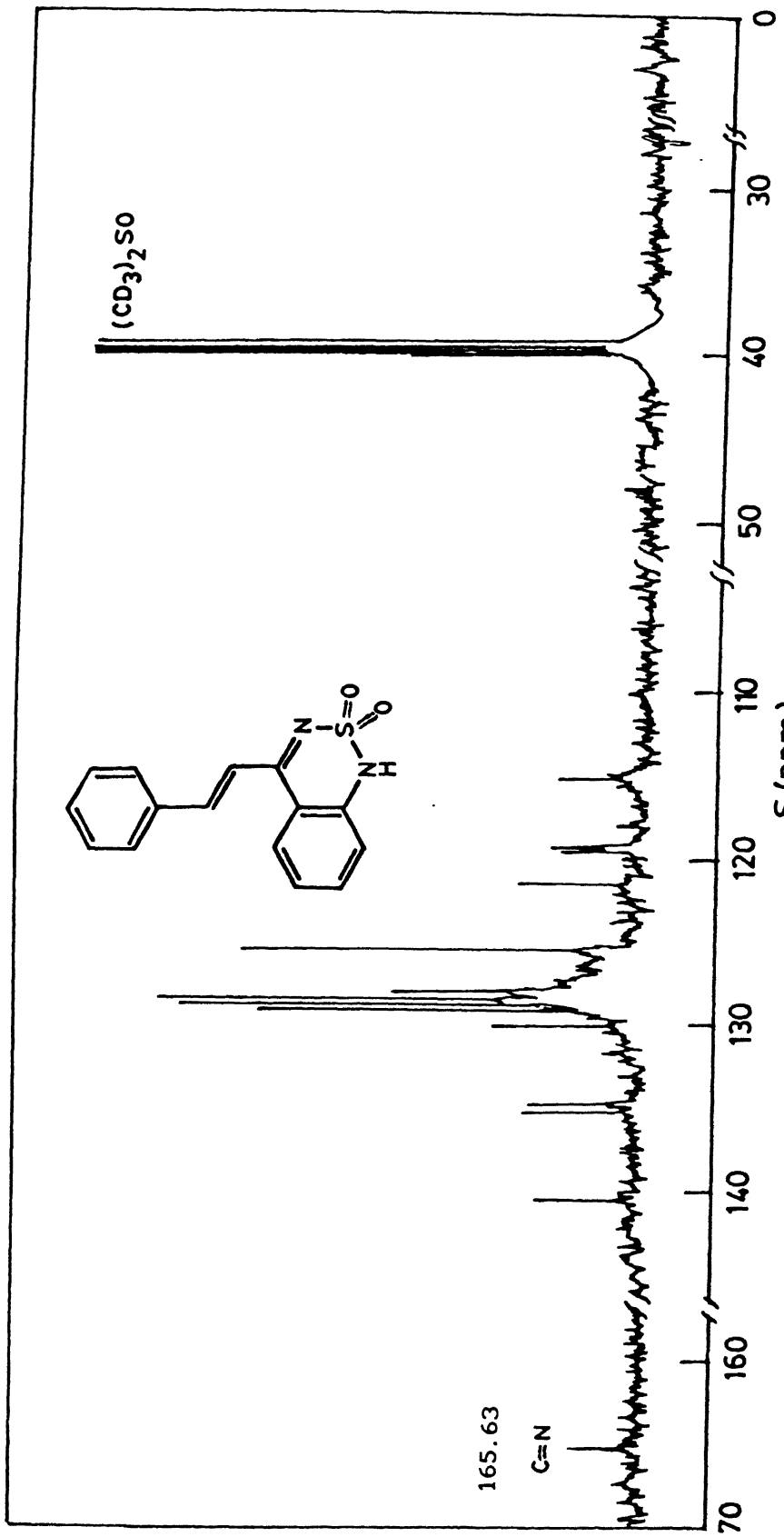


FIG. IV.7 ^{13}C-NMR SPECTRUM OF 19 a

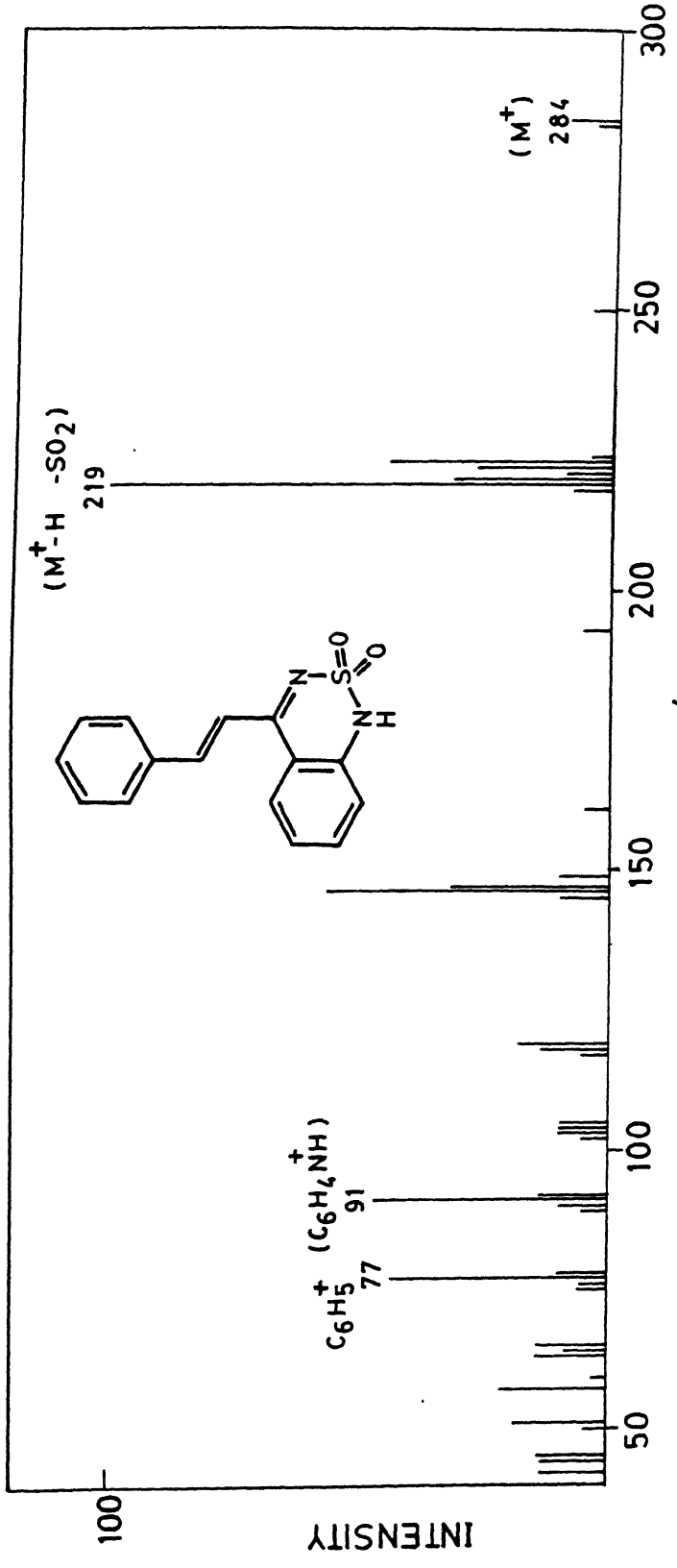


FIG. IV.8 MASS SPECTRUM OF 19a

carbon atoms respectively. The IR and ^{13}C-NMR spectral data of **19a** were compared with 1,2,6-thiadiazine-1,1-dioxide[21] and found to be in good agreement.

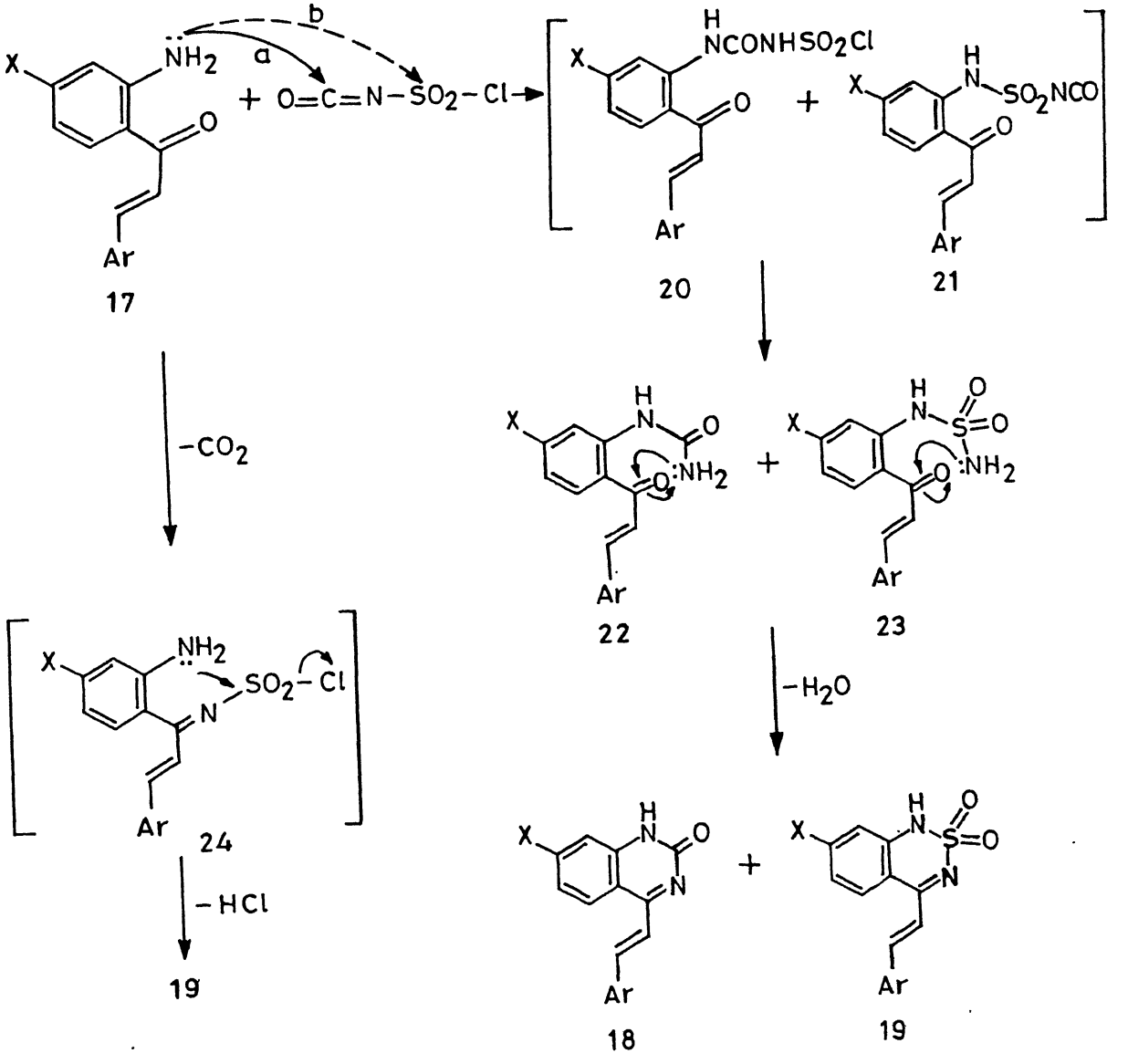
The final proof for the formation of **19a** comes from the mass spectral data (Fig. IV.8). The molecular ion peak and base peak appeared at m/z: 284 and 219 ($M^+ - H - SO_2$) respectively. Other important peaks are at m/z: 146, 102 ($C_6H_4C{=}N^{+\cdot}$) and 91 ($C_6H_4NH^{+\cdot}$). The elemental analysis of **19a** is found to be in good agreement with the molecular formula $C_{15}H_{12}N_2O_2S$.

Based on the above analytical and spectral characteristics the structure of **19a** was assigned as: 4-styryl-1H-2,1,3-benzothiadiazine--2,2-dioxide.

The rational for the formation of **18a** and **19a** is shown in Scheme IV.3.2. The mechanism involves the nucleophilic attack of amino group of chalcone **17** on the CSI in two different ways. According to path (a), the lone pair of amino function of **17** attacks the isocyanate group of CSI to give N-chlorosulfonyl urea derivative **20** as an intermediate. Path (b) involves the nucleophilic attack of amino group of chalcone on the sulfonyl group of CSI resulting in the formation of another class of reactive isocyanate **21**. The intermediates, viz., **20** and **21** undergo alkaline hydrolysis to produce non-isolable compounds, urea **22** and sulfonyl urea **23** derivatives. Compounds **22** and **23** undergo intramolecular cyclization with the carbonyl group to form 4-styryl-2(1H)-quinazolinone and 4-styryl-1H-2,1,3-benzothiadiazine-2,2-dioxide respectively.

2'-Amino-4-nitrochalcone (**17f**) on treatment with CSI under similar reaction conditions, gave only one product viz., 4-(4-nitrostyryl)-2(1H)-quinazolinone (**19f**). This suggests that

SCHEME IV.3.2


b
a
+ O=C=N-SO2-Cl
NH2
X
O
Ar
17
H
NCONHSO2Cl
20
H
N
SO2NCO
21
-CO2
H
N
O
:NH2
22
S
23
-H2O
NH2
SO2-Cl
N
24
-HCl
19
18
19

benzothiadiazine-2,2-dioxide derivatives are formed by another mechanism. In light of the reaction of CSI with carbonyl compounds forming iminosulfonyl chloride,[2,22] the mechanism of reaction is proposed as follows: The carbonyl group of **17f** reacts with isocyanate function of CSI to give the corresponding iminosulfonyl chloride **24** with the elimination of carbon dioxide. This follows the intramolecular cyclization with amino group resulting in the formation of **19(a-f)**. The strong electron accepting group *viz.*, nitro, at the *para* position of the 3-phenyl substituent does not favour the formation of iminosulfonyl chloride intermediate and hence the reaction does not give benzothiadiazine derivative **19f**.

In conclusion it may be pointed out here that the present reaction proves the formation of 2(1H)-quinazolinones and 1H-2,1,3--benzothiadiazine-2,2-dioxide derivatives in accord with our expectations. Both the compounds **18(a-g)** and **19(a-f)** contain a substituted vinyl group on position-4, which can be further functionalized. 4-Substituted quinazoline-2-ones and 2,1,3-benzothiadiazines are of pharmacological importance, and hence the present reaction provides a simple synthetic route to these heterocycles.

IV.4. EXPERIMENTAL

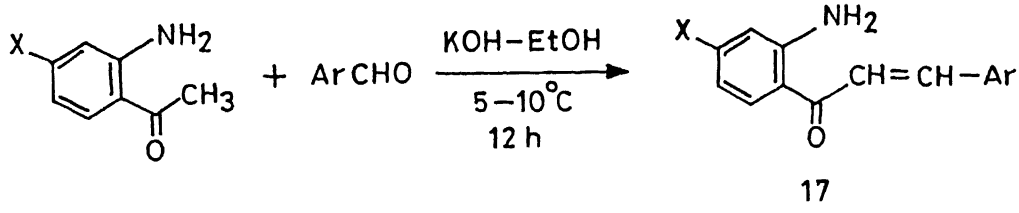
Refer to section II.4 for experimental details about the instruments used in these experiments.

IV.4.1 Starting Materials

Chlorosulfonyl isocyanate (Fluka, A.G.; Switzerland), dichloromethane (distilled from P_2O_5) and acetonitrile (dried over CaH_2) were used in this investigation. 2'-Aminochalcones were

prepared by the known procedures[5,6] by the condensation of 2'-aminoacetophenones with appropriate benzaldehydes as shown in Scheme IV.4.1.

SCHEME IV.4.1



17

IV.4.2 Synthesis of 1-(2-aminophenyl)-3-phenyl-2-propen-1-one (2-aminochalcone) (17a):

2'-Aminoacetophenone (2.70 g, 20 mmol) was added to a solution of benzaldehyde (2.12 g, 20 mmol) in absolute ethanol (20 ml) containing catalytic amount of solid sodium hydroxide (2 pellets) at 0-5°C. The mixture was stirred at this temperature for 5h and then kept in refrigerator overnight. Orange precipitate obtained was filtered and washed with a little ice-cold ethanol. Crystallization from small amount of ethanol afforded the pure 2'-aminochalcone. Yield: 2.36 g (53%); m.p.: 71°C (71-72°C).

The other substituted 2'-aminochalcones **17(b-e)** and **17g** were prepared using the same procedure given in section IV.4.2. 2'-Amino-5'-bromochalcone (**17f**) was prepared from 2'-aminochalcone (**17a**) and one mole equivalent of bromine[6]. The data about the 2'-aminochalcones, prepared in the above manner, are summarized in Table IV.1.

Table IV.1

2'-AMINOCHALCONES

CHALCONES 17	SUBSTITUENTS Ar	X	SOLVENT FOR CRYSTALLIZATION	YIELD (%)	m.p.°C [LIT.]	REF NO.
a	C_6H_5	H	EtOH	63	71[71-72]	5
b	*p*-$CH_3OC_6H_4$	H	EtOH	68	92-93	
C	*p*-$CH_3C_6H_4$	H	EtOH	63	107	
d	*p*-ClC_6H_4	H	EtOH	57	102-103	
e	2-Furyl	H	MeOH	55	72	
f	C_6H_5	Br	EtOH	70	147[150]	6
g	*p*-$NO_2C_6H_4$	H	Benzene	51	181	

IV.4.3 Reaction of 2'-aminochalcone (17a) with CSI

(General procedure)

To a stirred solution of **17a** (0.67 g, 3 mmol) in acetonitrile (10 ml) was added dropwise a solution of CSI (0.29 ml, 3.3 mmol) in dichloromethane (5 ml) at -10°C. The solution acquired dark brown color. Stirring was continued, at this temperature, for 2h and then at room temperature for ~10h. The resulting reaction mixture was concentrated, and the residue was dissolved in acetone-water (19:1, 20 ml) and hydrolysed with aqueous KOH solution (2 ml, 5%). The reaction mixture was stirred at room temperature for 24h, neutralized with dil. HCl and diluted with water (20 ml). A yellow precipitate was obtained which was filtered off and washed with plenty of water. The precipitate was dried and submitted to flash column

chromatography [silica gel, eluents: benzene-dichloromethane (1:1) and dichloro- methane-methanol (9:1)]. The two products, **18a** and **19a**, separated by chromatography, were recrystallized from ethanol. Yield, melting point, analytical and spectral data of compounds **18a** and **19a** are given below.

4-Styryl-2(1H)-quinazolinone (18a)

Yield: 0.32 g (43%); m.p.: 225^{0}C.

Anal. for $C_{16}H_{12}N_2O$: Calcd: C, 77.39; H, 4.87; N, 11.28 %
Found: C, 77.23; H, 4.95; N, 11.36 %

IR (KBr) ν_{max} : 3430, 1664, 1607, 1588, 1492, 1110, 815, 740 cm.$^{-1}$

Mass m/z (rel. int.) : 249 (M^++1, 19), 248 (M^+, 72), 247 (M^+-1, 100), 219 (13), 206 (9), 205 (3), 204 (10), 171 (77), 160 (17), 102 (14).

^{1}H-NMR (DMSO-d_6) δ : 7.14-8.58 (m, 11H), 11.89 (brs, 1H).

^{13}C-NMR (DMSO-d_6) δ : 114.71, 115.25, 120.57, 122.08, 126.30, 128.67, 128.87, 130.08, 135.06, 135.27, 140.76, 143.22, 155.04, 168.40.

4-Styryl-1H-2,1,3-benzothiadiazine-2,2-dioxide (19a)

Yield: 0.14g (16%); m.p.: 237-240^{0}C.

Anal. for $C_{15}H_{12}N_2O_2S$: Calcd: C, 63.36; H, 4.26; N, 9.85 %
Found: C, 63.17; H, 4.42; N, 10.07 %

IR (KBr) ν_{max} : 3210, 1625, 1600, 1350, 1330, 1160, 755, 700 cm.$^{-1}$

Mass m/z (rel. int.) : 284 (M^+, 14), 283 (M^+-1, 8), 250 (8), 223 (47), 222 (30), 220 (34), 219 (100), 161

(11), 147 (35), 146 (57), 102 (10), 91 (52).

^{1}H-NMR (DMSO-d_6) δ : 6.51-7.89 (m, 12H).

^{13}C-NMR (DMSO-d_6) δ : 115.17, 119.21, 121.54, 125.56, 128.07, 128.56, 128.82, 129.18, 130.03, 134.63, 135.10, 140.40, 165.63.

IV.4.4 Reaction of 4-methoxy-2'-aminochalcone (17b) with CSI

Chalcone **17b** (0.76 g, 3 mmol) and CSI (0.29 ml, 3.3 mmol) were treated in an analogous manner and chromatographed as described earlier (cf. IV.4.3). The two products **18b** and **19b**, separated by chromatography were crystallized from dichloromethane and methanol respectively. Analytical and spectral data of **18b** and **19b** are given below.

4-(4-Methoxystyryl)-2(1H)-quinazolinone (18b)

Yield: 0.35 g (42%); m.p.: 248-250°C.

Anal. for $C_{17}H_{14}N_2O_2$: Calcd: C, 73.36; H, 5.07; N, 10.07 %
Found: C, 73.31; H, 5.16; N, 10.22 %

IR (KBr) ν_{max} : 3420, 1660, 1575, 1505, 1170, 1025, 820, 750 $cm.^{-1}$

Mass m/z (rel. int.) : 279 (M^++1, 15), 278 (M^+, 68), 277 (M^+-1, 100), 263 (48), 247 (24), 235 (9), 234 (14), 171 (37), 121 (12), 119 (5), 118 (13), 102 (9).

^{1}H-NMR (DMSO-d_6) δ : 3.87 (s, 3H), 6.95-8.44 (m, 10H), 11.54 (brs, 1H).

^{13}C-NMR (DMSO-d_6) δ : 55.30, 114.35, 114.68, 115.21, 117.85, 121.94, 126.17, 127.95, 130.47, 134.81, 140.70, 143.12, 155.07, 160.95, 168.49.

4-(4-Methoxystyryl)-1H-2,1,3-benzothiadiazine-2,2-dioxide (19b)

Yield: 0.19 g (20%); m.p.: 220°C.

Anal. for $C_{16}H_{14}N_2O_3S$: Calcd: C, 61.13; H, 4.49; N, 8.91 %
Found: C, 60.89; H, 4.61; N, 9.06 %

IR (KBr) ν_{max} : 3205, 1630, 1595, 1350, 1255, 1160, 1030, 835, 765 cm.$^{-1}$

Mass m/z (rel. int.) : 315 (M^++1, 3), 314 (M^+, 10), 280 (16), 250 (46), 235 (30), 206 (18), 146 (22), 121 (100), 91 (73).

^{1}H-NMR (DMSO-d_6) δ : 3.86 (s, 3H), 6.83-8.19 (m, 10H), 11.57 (brs, 1H).

^{13}C-NMR (DMSO-d_6) δ : 54.99, 114.03, 114.48, 117.30, 117.83, 122.10, 127.46, 127.55, 128.76, 131.05, 135.11, 142.59, 142.91, 158.59, 161.55.

IV.4.5 Reaction of 2'-amino-4-methylchalcone (17c) with CSI

Reaction of CSI (0.20 ml, 2.2 mmol) with **17c** (0.475 g, 2 mmol) was carried out using the same procedure as described in section IV.4.3. Reaction mixture was concentrated and residue was treated with aqueous KOH in acetone-water. Resulting solution was neutralized with dilute HCl and extracted with dichloromethane (3x25 ml). The extract was washed with water, dried (Na_2SO_4) and evaporated to dryness. The solid obtained was chromatographed on silica gel using, ether-dichloromethane (1:1) and dichloromethane-methanol (9:1) as

eluents to give two products 18c and 19c. Compound 18c was recrystallized from dichloromethane in yellow crystals. The other product 19c was crystallized from methanol as yellow solid. Analytical and spectral data of 18c and 19c are given below.

4-(4-Methylstyryl)-2(1H)-quinazolinone (18c)

Yield: 0.25 g (48%); m.p.: 252^{o}C

Anal. for $C_{17}H_{14}N_2O$: Calcd: C, 77.84; H, 5.38; N, 10.68 %
Found: C, 77.76; H, 5.49; N, 10.75 %

IR (KBr) ν_{max} : 3420, 1675, 1630, 1590, 1250, 840, 745 cm.$^{-1}$

Mass m/z (rel. int.) : 263 (M^++1, 17), 262 (M^+, 59), 261 (M^+-1, 100), 247 (53), 220 (13), 219 (6), 171 (65), 115 (12), 91 (16).

^{1}H-NMR (DMSO-d_6) δ : 2.52 (s, 3H), 6.91-8.47 (m, 10H), 11.70 (brs, 1H).

4-(4-Methylstyryl)-1H-2,1,3-benzothiadiazine-2,2-dioxide (19c)

Yield: 0.11 g (18%); m.p.: 224-226^{o}C.

Anal. for $C_{16}H_{14}N_2O_2S$: Calcd: C, 64.41; H, 4.73; N, 9.39 %
Found: C, 64.29; H, 4.56; N, 9.58 %

IR (KBr) ν_{max} : 3220, 1620, 1590, 1330, 1250, 1145, 1020, 830, 760 cm.$^{-1}$

Mass m/z (rel. int.) : 298 (M^+, 23), 297 (M^+-1, 9), 283 (13), 264 (7), 234 (39), 233 (100), 146 (56), 102 (7), 91 (21).

^{1}H-NMR (DMSO-d_6) δ : 2.46 (s, 3H), 6.62-8.12 (m, 10H), 11.45 (brs, 1H).

IV.4.6 Reaction of 2'-amino-4-chlorochalcone (17d) with CSI

The reaction of **17d** (0.52 g, 2 mmol), with CSI (0.20 ml, 2.2 mmol) was carried out using the same procedure as described in section IV.4.3. Elution of the column with benzene-dichloromethane (1:1) gave **18d**, which was recrystallized from dichloromethane as yellow crystalline solid. Further elution with dichloromethane-methanol (9:1) afforded **19d**. Compound **19d** was recrystallized from methanol in pure form. Analytical and spectral data of **18d** and **19d** are given below.

4-(4-Chlorostyryl)-2(1H)-quinazolinone (18d)

Yield: 0.21 g (37%); m.p.: 242-246^{0}C (dec.).

Anal. for $C_{16}H_{11}ClN_2O$: Calcd: C, 67.91; H, 3.92; N, 9.91 %
Found: C, 67.72; H, 3.84; N, 10.06 %

IR (KBr) ν_{max} : 3430, 1655, 1620, 1575, 1485, 1360, 1010, 810, 745 cm.$^{-1}$

Mass m/z (rel. int.) : 284 (M^++2, 21), 283 (M^++1, 47), 282 (M^+, 52), 281 (M^+-1, 100), 255 (4), 253 (9), 241 (5), 239 (17), 171 (43), 127 (2), 125 (7), 102 (31), 91 (82).

^{1}H-NMR (DMSO-d_6) δ : 6.89-8.42 (m, 10H), 11.86 (brs, 1H).

4-(4-Chlorostyryl)-1H-2,1,3-benzothiadiazine-2,2-dioxide (19d)

Yield: 0.07 g (11%); m.p.: 204^{0}C.

Anal. for $C_{15}H_{11}ClN_2O_3S$: Calcd: C, 56.51; H, 3.48; N, 8.79 %
Found: C, 56.23; H, 3.74; N, 8.92 %

IR (KBr) ν_{max} : 3260, 1630, 1580, 1480, 1330, 1260, 1145, 1010, 815, 745 cm.$^{-1}$

Mass m/z (rel. int.) : 320 (M^++2, 5), 318 (M^+, 21), 317 (M^+-1, 12), 284 (15), 282 (78), 255 (14), 253 (38), 161 (19), 159 (47), 146 (100), 102 (29), 91 (79).

^{1}H-NMR (DMSO-d_6) δ : 6.72-8.12 (m, 10H), 11.74 (brs, 1H).

IV.4.7 Reaction of 3-(2-furyl)-1-(2-aminophenyl)-2-propen-1-one (17e) with CSI

The reaction was carried out using chalcone **17e** (0.85 g, 4 mmol) and CSI (0.40 ml, 4.4 mmol) in a manner similar to the one described earlier (cf. IV.4.3). Compound **18e** was obtained as dark brown solid which was recrystallized from methanol as reddish crystals. The other compound **19e** was obtained by column chromatography. However, it was not further crystallized since it was found to be insoluble in common solvents. Yield, melting point, analytical and spectral data of **18e** and **19e** are given below.

4-[β-(2-furyl)vinyl]-2(1H)-quinazolinone (18e)

Yield: 0.53 g (56%); m.p.: 205^{0}C.

Anal. for $C_{14}H_{10}N_2O_2$: Calcd: C, 70.57; H, 4.23; N, 11.76 %
Found: C, 70.39; H, 4.31; N, 11.88 %

IR (KBr) ν_{max} : 3430, 1660, 1580, 1350, 1020, 750 cm.$^{-1}$

Mass m/z (rel. int.) : 239 (M^++1, 14), 238 (M^+, 100), 237 (M^+-1, 44), 210 (74), 209 (34), 197 (30), 196 (36), 184 (83), 171 (16), 102 (14).

^{1}H-NMR (DMSO-d_6) δ : 6.58-8.19 (m, 9H), 11.57 (brs, 1H).

4-[β-(2-furyl)vinyl]-1H-2,1,3-benzothiadiazine-2,2-dioxide (19e)

Yield: 0.25 g (23%); m.p.: 245°C.

Anal. for $C_{13}H_{10}N_2O_3S$: Calcd: C, 56.92; H, 3.67; N, 10.21 %
Found: C, 56.74; H, 3.88; N, 10.32 %

IR (KBr) ν_{max} : 3225, 1625, 1580, 1510, 1340, 1215, 1160, 1020, 760 $cm.^{-1}$

Mass m/z (rel. int.) : 275 (M^++1, 8), 274 (M^+, 61), 273 (M^+-1, 2), 233 (16), 220 (25), 210 (25), 209 (35), 193 (61), 181 (65), 169 (29), 156 (45), 102 (15), 91 (81), 41 (100).

^{1}H-NMR (DMSO-d_6) δ : 6.42-8.18 (m, 9H), 11.61 (brs, 1H).

IV.4.8 Reaction of 5'-bromo-2'-aminochalcone (17f) with CSI

Compound **17f** (0.604 g, 2 mmol) on treatment with CSI (0.20 ml, 2.2 mmol) in the usual way (cf. section IV.4.3) gave a brown colored solid. The above solid on hydrolysis with aq. KOH in acetone-water and neutralization with dil. HCl gave a dark red residue. This on flash column chromatography (silica gel, eluents: benzene-dichloromethane (1:1) and dichloromethane-methanol (9:1)) furnished **18f** and **19f**. Compound 18f was recrystallized from ethyl acetate-ether as pale yellow crystals. The other product **19f**, however could not be further purified since it is insoluble in most of the common solvents. Structures of compounds **18f** and **19f** were confirmed on the basis of their analytical and spectral data which are given below.

6-Bromo-4-styryl-2(1H)-quinazolinone (18f)

Yield: 0.25 g (38%); m.p.: 232°C.

Anal. for $C_{16}H_{11}BrN_2O$: Calcd: C, 58.73; H, 3.39; N, 8.56 %

Found: C, 58.48; H, 3.56; N, 8.73 %

IR (KBr) ν_{max} : 3400, 1674, 1632, 1585, 1472, 1289, 1041, 825, 764, 700 $cm.^{-1}$

^{1}H-NMR (DMSO-d_6) δ : 6.85-7.86 (m, 10H), 11.78 (brs, 1H).

6-Bromo-4-styryl-1H-2,1,3-benzothiadiazine-2,2-dioxide (19f)

Yield: 0.06 g (8%); m.p.: 220^{0}C.

Anal. for $C_{15}H_{11}BrN_2O_2S$: Calcd: C, 49.60; H, 3.04; N, 7.71 %

Found: C, 49.05; H, 3.52; N, 8.09 %

IR (KBr) ν_{max} : 3255, 1632, 1545, 1328, 1256, 1164, 825, 771, 696 $cm.^{-1}$

^{1}H-NMR (DMSO-d_6) δ : 6.76-8.16 (m, 10H), 11.36 (brs, 1H).

IV.4.9 Reaction of 2'-amino-4-nitrochalcone (17g) with CSI

A solution of CSI (0.29 ml, 3.3 mmol) in dichloromethane (3 ml) was added to a stirred solution of **17g** (0.804 g, 3 mmol) in acetonitrile (10 ml) at 0^{0}C. Solution was brought-up to ambient temperature and stirred further for 24h. Resulting solution was evaporated in *vacuo* and treated with dil. KOH and subsequently neutralized in the usual way. Dilution of reaction mixture with water gave a dark red precipitate which was filtered and dried and upon crystallization from methanol furnished the compound **18g** as a red solid.

4-(4-Nitrostyryl)-2(1H)-quinazolinone (18g)

Yield: 0.31 g (35%); m.p.: 216-218^{0}C.

IR (KBr) ν_{max} : 3405, 1680, 1595, 1515, 1340, 855, 750 $cm.^{-1}$

^{1}H-NMR (DMSO-d_6) δ : 6.56-8.41 (m, 10H), 11.41 (brs, 1H).

REFERENCES

1. K. Clauss, H.J. Friedrich, H. Jensen, *Justus Liebigs Ann. Chem.*, 1974, 561.
2. D.N.Dhar, G. Mehta, S.C.Suri, *Ind. J. Chem.*, 1976, **14B**, 477.
3. D.N. Dhar, A.K. Bag, *Ind. J. Chem.*, 1983, **22B**, 627.
4. S. Wattanasin, W.S. Murphy, *Synthesis*, 1980, 647.
5. J.A. Donnelly, D.F. Farrell, *J. Org. Chem.*, 1990, **55**, 1757.
6. A.L. Tökés, G. Janzsó, *Synth. Commun.*,1989, **19**, 3159.
7. K. Ischizumi, K. Mori, M. Yamamoto, M. Koshiba, S. Inaba, H. Yamamoto, *Ger. Offen*, 2, 345, 030, 1974; *Chem. Abstr.*, 1974, **80**, 146193p.
8. S. Gabriel, R. Stelzner, *Chem. Ber.*, 1896, **29**, 1300.
9. E.B. Skibo, *J. Org. Chem.*, 1985, **50**, 4861.
10. V.T. Bandurco, S.D. Levine, D.M. Mulvey, A.J. Tobia, *Brit. UK Pat. Appl.* GB, 2, 127, 823, 1984; *Chem. Abstr.*, 1984, **101**, 151871q.
11. M. Schleuder, P.H. Richter, G. Kreher, O. Morgenstern, *Pharmazie*, 1991, **46**, 748; *Chem. Abstr.*, 1992, **116**, 128884x.
12. J.B. Wright, *J. Org. Chem.*, 1965, **30**, 3960.
13. E. Cohen, B. Klarberg, *J. Am. Chem. Soc.*, 1962, **84**, 1994.
14. A. Kamal, K.R. Rao, P.B. Sattur, *Synth. Commun.*, 1980, **10**, 799.
15. A.K. Bag, Ph.D. Thesis, I.I.T. Kanpur, 1984.
16. R.V.Coombs, R.P. Daina, M. Denzer, G.E. Hardtmann, B. Huegi, G. Koletar, J. Koletar, H. Oh, E. Jukniewicz, *J. Med. Chem.*, 1973, **16**, 1237; *Chem. Abstr.*, 1973, **79**, 142798w.

17. R.K. Russell, M.A. Appollina, V. Bandurco, D.W. Combs, R.M. Kanojia, R. Mallory, E. Malloy, J.J. McNally, D.M. Mulvey, Y Gray-Nunez, M.S. Rampulla, R.A. Rampulla, S.A. Sisk, L. Williams, S.D. Levine, S.C. Bell, E.C. Giardino, R. Faltico, A.J. Tobia *Eur. J. Med. Chem.*, 1992, **27**, 277.

18. W.J. Houlihan, *U.S. Pat.*, 3, 278, 532, 1966; *Chem. Abstr.*, 1966, **65**, 20154c.

19. H. Culbertson, J.C. Decius, B.E. Christensen, *J. Am. Chem. Soc.*, 1952, **74**, 4834.

20. J. Elguero, C. Ochoa, M. Stud, C. Esteban-Calderon, M. Martinez-Ripoll, J.P. Fayet, M.C. Vertut, *J. Org. Chem.*, 1982, **47**, 536.

21. V.J. Arán, P. Goya, C. Ochoa, *Adv. Heterocycl. Chem.*, 1988, **44**, 81.

22. S.P. Joseph, K.S.K. Murthy, D.N. Dhar, *Synth. Commun.*, 1989, **19**, 417.

VITAE

Born on January 15, 1966 in Sandi (Hardoi; U.P.), Pramod Kumar had his early education in Sandi and completed schooling at Government Inter College, Hardoi in 1982. He obtained the degree of Bachelor of Science from Christian College Lucknow (University of Lucknow) in 1984 and the degree of Master of Science from University of Lucknow in 1986.

He was a Research Assistant in the Department of Pathology, King George's Medical College Lucknow in 1986, and joined the Ph.D. programme in the Department of Chemistry Indian Institute of Technology Kanpur, in July 1988. Presently he is a Senior Research Scholar in the same department